Department of General Practice and Primary Health Care
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RELATIONSHIP OF NEUROPSYCHIATRIC SYMPTOMS WITH FALLS, PSYCHOTROPIC DRUG USE AND QUALITY OF LIFE AMONG PEOPLE WITH DEMENTIA

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“It’s not what you look at that matters, it’s what you see”.

- *Henry David Thoreau*

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Roitto HM, Kautiainen H, Öhman H, Savikko N, Strandberg TE, Raivio M, Laakkonen ML, Pitkälä KH. Relationship of Neuropsychiatric Symptoms with Falls in Alzheimer's Disease - Does Exercise Modify the Risk? J Am Geriatr Soc. 2018;66:2377-2381. doi: 10.1111/jgs.15614.

II Roitto HM, Kautiainen H, Aalto UL, Öhman H, Laurila J, Pitkälä KH. Fourteen-Year Trends in the Use of Psychotropic Medications, Opioids, and Other Sedatives Among Institutionalized Older People in Helsinki, Finland. J Am Med Dir Assoc. 2019;20:305-311. doi: 10.1016/j.jamda.2018.12.022.

III Roitto HM, Kautiainen H, Laurila J, Pitkälä KH. Severity of both neuropsychiatric symptoms and dementia is associated with quality of life in nursing home residents. Eur Geriatr Med 2019;10:793–800. doi: 10.1007/s41999-019-00213-0.

IV Roitto HM, Öhman H, Salminen K, Kautiainen H, Laurila J, Pitkala KH. Neuropsychiatric Symptoms as Predictors of Falls in Long-Term Care Residents with Cognitive Impairment. J Am Med Dir Assoc. 2020. doi: 10.1016/j.jamda.2020.04.003.

The publications are referred to in the text by their roman numerals. They are reprinted with the kind permission of the publishers.

ABBREVIATIONS

Aβ42	Amyloid-beta peptide-42, a biomarker in AD diagnostics
AD	Alzheimer's disease
ADL	Activities of daily living scale
AGS	American Geriatrics Society
ALF	Assisted-living facility
APA	American Psychiatry Association
APOE	Apolipoprotein E
ATC	Anatomical Therapeutic Chemical (classification)
BI	Barthel Index
BPSD	Behavioral and psychological symptoms of dementia
CAIDE	Cardiovascular Risk Factors, Aging and Dementia (study)
CCI	Charlson comorbidity index
CDR	Clinical dementia rating
ChEI	Cholinesterase inhibitor
CMAI	Cohen-Mansfield Agitation Inventory
CMS	Centers for Medicare & Medicaid Services
CNS	Central nervous system
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy bodies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FINALEX	Finnish Alzheimer disease exercise trial
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FTLD	Frontotemporal lobar degeneration
HRQoL	Health-related quality of life
IADL	Instrumental activities of daily living scale
ICD-10	International Classification of Diseases, tenth edition
ICD-11	International Classification of Diseases, eleventh edition
IRR	Incidence rate ratio
LATE	Limbic-predominant age-related TDP-43 encephalopathy
MBI	Mild behavioral impairment
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MNA	Mini-Nutritional Assessment
MRI	Magnetic resonance imaging
NCD	Neurocognitive disorder
NH	Nursing home
NIA-AA	National Institute on Aging and Alzheimer's Association

NINCDS-ARDRA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
NPS(s)	Neuropsychiatric symptom(s)
OR	Odds ratio
PART	Primary age-related tauopathy
PDD	Parkinson´s disease dementia
P-TAU	Phosphorylated tau protein, a biomarker in AD diagnostics
PYR	Person-year
QoL	Quality of life
QT	Measurement that represents the total time from ventricular depolarization to complete repolarization
RCT	Randomized controlled trial
SD	Standard deviation
SPPB	Short Physical Performance Battery
SSRI	Serotonin selective reuptake inhibitor
TAU	Tau protein, a biomarker in AD diagnostics
TCA	Tricyclic antidepressant
TDP	Transactivation response DNA-binding protein
VAD	Vascular dementia
VCI	Vascular cognitive impairment
WHO	World Health Organization

ABSTRACT

Background: Dementia is characterized not only by cognitive and functional decline, but also by neuropsychiatric symptoms (NPSs). These affect almost all people with dementia during the course of the disease. NPSs are associated with impaired health-related quality of life (HRQoL) and admission to long-term care. People with dementia have an elevated risk of falling. Fall risk has been associated with impaired mobility, some NPSs such as depression and anxiety, and the use of psychotropic drugs. In long-term-care settings the prevalence of use of any psychotropic drug has been reported to be very high. There is a scarcity of studies on the interplay between NPSs, psychotropics, falls, and HRQoL

Objectives: This study, comprised of four sub-studies, was aimed at examining the relationships between NPSs, falls, psychotropic drug use and HRQoL among people with dementia. The relationship between NPSs and falls was explored in two different populations: home-dwelling older adults with Alzheimer's disease (AD) (Study I), and institutionalized older adults with cognitive impairment (Study IV). Study I concerned how long-term exercise modifies the risk of falling in community-dwelling people with AD and NPSs. Study IV was carried out to explore whether or not psychotropic drug use modifies the relationship between NPSs and falls. Study III concerned the association between NPSs and HRQoL, and, further, how the severity of dementia modifies this relationship. In addition, Study II concerned temporal trends in the prevalence of use of psychotropics and opioids, and sedative load in long-term-care settings over a 14-year period in relation to the residents' dementia status.

Participants: Study I was a secondary analysis of a randomized controlled trial, FINALEX. All the participants from the original FINALEX trial whose spousal caregivers had completed the Neuropsychiatric Inventory (NPI) at baseline and who had had at least three months of follow-up were included in this study (n=179). Study II is based on Helsinki Nutrition and Medication studies conducted in 2003–2018. It comprised four cross-sectional studies in institutional settings in Helsinki. The participants were residents in nursing homes (NHs) in 2003 (n=1987), 2011 (n=1576), and 2017 (n=791) and in assisted-living facilities (ALFs) in 2007 (n=1377), 2011 (n=1586), and 2017 (n=1752). The participants of Studies III and IV were a random sample of long-term-care residents aged 65 years and older in Helsinki (n=532).

Measures: NPSs were measured with the NPI. In Studies III and IV participants were placed in three groups: no significant NPSs (NPI points 0–3), low-NPS burden (4–12 points) and high-NPS burden (NPI >12 points). The

severity of dementia was measured by using Clinical Dementia Rating (CDR). HRQoL was measured by using the 15D instrument. Falls were recorded in daily-falls diaries in Study I and collected from medical records in Study IV over a one-year period. Data on demographics, diagnoses and medication were collected from medical records. Types of medication were classified according to Anatomical Therapeutic Chemical (ATC) classification.

Results: Mean ages ranged from 78 to 84 years in four large samples. The participants had a high number of comorbidities and were given a high number of drugs (mean range 6.9-8.6). The severity of cognitive impairment varied. Most of the participants in Study I had mild to moderate dementia (CDR 0.5–2), whereas almost all long-term-care residents had moderate to severe dementia (CDR 2–3) (Studies II–IV).

In Studies I and IV falls had a clear relationship with NPSs measured by the total NPI score. In Study I the incidence of falls increased linearly with NPI score in the control group. The fall rate was 2.87 per person-years (95% Cl 2.43–3.35) in the control group, whereas the exercise intervention group showed no such relationship with NPI score and had a fall rate of 1.48 per person-years (95% Cl 1.26–1.73). In Study IV the NPI total score had a curvilinear association with the incidence rate of falls per person-years. Using the no-significant-NPSs group as a reference, the low-NPS-burden group had an IRR per SD for falls of 1.64 (95% Cl 1.27–2.12), whereas in the high-NPS-burden group the IRR per SD was 2.43 (95% Cl 1.91–3.08). Psychotropics did not modify the relationship between NPSs and falls. Psychosis and hyperactivity subsyndromes were associated with higher IRRs of falls, whereas apathy and affective symptoms were not.

In Study III the severity of NPSs was significantly associated with better HRQoL (15D measures). This seemed to be related to better physical functioning and greater vitality. Residents with severe dementia (CDR 3) had worse HRQoL than residents with mild-to-moderate dementia (CDR <3). There was a significant interaction between NPI and CDR scores ($p=0.037$ for NPI, $p<0.001$ for CDR and $p<0.001$ for interaction).

In Study II the prevalence of use of all psychotropics decreased significantly in NHs (from 81% to 61%), whereas in ALFs there was no such trend (from 65% to 64%). There was a significant increase in opioid use in both settings. Residents with dementia used fewer psychotropics and opioids than those without dementia in both settings and at all time points.

Conclusions: Neuropsychiatric symptoms and their severity are associated with fall risk. Evaluation of NPSs, especially NPS severity and neuropsychiatric subsyndromes, should be part of comprehensive assessment when aiming to prevent falls in long-term-care residents with cognitive impairment. Exercise has the potential to reduce the risk of falls associated with NPSs. The severity of NPSs and dementia are both important factors determining HRQoL. NPSs have a distinct impact on HRQoL at different stages of dementia. The prevalence of psychotropic use has decreased over the last 14 years in NHs in Helsinki, but at the same time the rates of opioid use have increased in both NHs and ALFs, leading to a high overall sedative load among long-term-care residents.

TIIVISTELMÄ

Tutkimuksen tausta: Muistisairauksiin liittyy muistin ja toimintakyvyn heikentymisen lisäksi neuropsykiatrisia oireita. Niitä esiintyy lähes kaikilla muistisairauteen sairastuneilla jossakin vaiheessa sairautta. Neuropsykiatriset oireet yhdistyvät heikompaan terveyteen liittyvään elämänlaatuun ja lisääntyneeseen pitkäaikaishoidon tarpeeseen. Muistisairausta sairastavilla on suurempi kaatumisriski kuin ei-muistisairailla. Kaatumisriskiä lisäävät heikentynyt liikkumiskyky, eräät neuropsykiatriset oireet kuten masennus ja ahdistuneisuus, sekä psyykelääkkeiden käyttö. Pitkäaikaishoidossa psyykelääkkeiden käyttö on erittäin yleistä. Tutkimusnäyttö muistisairauksien neuropsykiatristen oireiden yhteyksistä psyykelääkkeiden käyttöön, kaatumisiin ja terveyteen liittyvään elämänlaatuun on vähäistä.

Tutkimuksen tavoitteet: Tämän tutkimuksen tavoitteena oli tutkia neuropsykiatristen oireiden yhteyksiä kaatumisiin, psyykelääkkeiden käyttöön ja terveyteen liittyvään elämänlaatuun muistisairailla ihmisillä. Tutkimus sisältää neljä osatyötä. Tutkimus selvitti neuropsykiatristen oireiden yhteyksiä kaatumisiin kahdessa eri kohortissa: kotona asuvilla Alzheimerin tautia sairastavilla ihmisillä (Osatyö I) sekä pitkäaikaishoidossa asuvilla ihmisillä, joilla oli todettu muistin heikentymää (Osatyö IV). Osatyö I tutki myös kuinka pitkäaikainen liikunta muokkaa kaatumisriskiä kotona asuvilla Alzheimerin tautia sairastavilla ihmisillä, joilla on neuropsykiatrisia oireita. Osatyö IV tutki muokkaako psyykelääkkeiden käyttö neuropsykiatristen oireiden ja kaatumisten yhteyttä. Osatyö III tutki neuropsykiatristen oireiden ja terveyteen liittyvän elämänlaadun yhteyttä ja kuinka muistisairauden vaikeusaste on siihen yhteydessä. Lisäksi, osatyö II tutki psyykelääkkeiden, opioidien ja sedatiivisen lääkekuorman muuttumista pitkäaikaishoidossa 14 vuoden seuranta-ajalla muistisairailla ja ei-muistisairailla.

Aineisto: Osatyö I oli alaryhmäanalyysi satunnaistetusta kontrolloidusta tutkimuksesta FINALEX:sta. Tutkimukseen otettiin mukaan kaikki tutkittavat, joiden puoliso oli täyttänyt NPI-mittarin (Neuropsychiatric Inventory) ja joiden seuranta-aika oli ainakin 3 kuukautta (n=179). Osatyö II perustuu Helsingin laitosvanhusten ravitsemus- ja lääketutkimukseen. Tutkittavat koostuivat neljästä suuresta poikkileikkauskohortista. Tutkittavat olivat asukkaita vanhainkodeissa vuosina 2003 (n=1987), 2011 (n=1576) ja 2017 (n=791) ja tehostetussa palveluasumisessa vuosina 2007 (n=1377), (n=1586) ja 2017 (n=1752). Osatöiden III ja IV tutkittavat olivat satunnaisotos kaikista yli 65 -vuotiaista pitkäaikaishoidon asukkaista Helsingissä (n=532).

Menetelmät: Neuropsykiatrisia oireet selvitettiin NPI mittarilla. Osatöissä III ja IV tutkittavat jaettiin kolmeen ryhmään neuropsykiatristen oireiden vaikeusasteen perusteella: ei merkitseviä oireita (NPI 0-3), lievä oirekuva (NPI 4-12), voimakas oirekuva (>12). Muistisairauden vaikeusaste mitattiin CDR-mittarilla (Clinical Dementia Rating). Terveyteen liittyvää elämänlaatua mitattiin 15D mittarilla. Kaatumiset rekisteröitiin puolisoiden reaaliajassa pitämiin kaatumispäiväkirjoihin osatyö I:ssä ja kerättiin potilastietojärjestelmästä osatyö IV:ssa vuoden seuranta-aikana. Demografiset tiedot, diagnoosit ja säännöllisesti käytössä oleva lääkitys vahvistettiin sairaskertomustiedoista. Lääkkeet koodattiin käyttämällä WHO:n ATC koodeja (Anatomical Therapeutic Chemical Classification).

Tulokset: Tutkittavien keski-ikä oli 78-84 vuotta neljässä eri kohortissa. Tutkittavilla oli useita pitkäaikaissairauksia ja pysyviä lääkityksiä. Säännöllisessä käytössä oli keskimäärin 6.9-8.6 lääkettä. Tutkittavien muistin oli lievemmin heikentynyt osatyössä I (CDR 0.5-2), kun taas pitkäaikaishoidossa lähes kaikilla oli vaikea-asteinen muistin heikentymä (CDR 2-3) (osatyöt II-IV).

Sekä osatyössä I että IV, kaatumiset olivat yhteydessä neuropsykiatrisiin oireisiin mitattuna NPI mittarilla. Osatyössä I kaatumisten määrä kasvoi lineaarisesti NPI pisteiden kanssa kontrolliryhmässä. Kaatumisia oli 2.87 henkilövuotta kohden (95%:n luottamusväli 2.43-3.35). Interventioryhmässä vastaavaa kasvua ei tapahtunut. Kaatumisia oli interventioryhmässä 1.48 henkilövuotta kohden (95%:n luottamusväli 1.26-1.73). Osatyössä IV kaatumisten ilmaantuvuusriski oli kaareutuvasti (kurvilineaarisesti) yhteydessä NPI pisteisiin. Kun ryhmää, jolla ei ollut merkitseviä neuropsykiatrisia oireita käytettiin referenssinä, niin lievästi neuropsykiatrisesti oireilevien kaatumisten ilmaantuvuusriski oli 1.64 (95%:n luottamusväli 1.27-2.12) ja voimakkaasti oireilevien taas 2.43 (95%:n luottamusväli 1.91-3.08). Psyykelääkkeiden käyttö ei muokannut kaatumisriskin ja neuropsykiatristen oireiden välistä yhteyttä. Neuropsykiatrisista oireryvästymistä psykoosi ja hyperaktiivisuus olivat yhteydessä suurempaan kaatumisriskiin, kun taas apatia ja tunneoireet eivät olleet.

Osatyössä III neuropsykiatristen oireiden voimakkuus oli merkitsevästi yhteydessä parempaan terveyteen liittyvään elämänlaatuun mitattuna 15D mittarilla. Tulos vaikutti olevan yhteydessä parempaan toimintakykyyn ja energisyyteen. Tutkittavilla, joilla oli vaikea-asteiseksi edennyt muistisairaus (CDR 3) oli huonompi elämänlaatu kuin, tutkittavilla, joiden muistisairaus oli

lievempi (CDR<3). NPI:n ja CDR:n välillä oli merkitsevä interaktio (p=0.037 NPI, p<0.001 CDR, p<0.001 interaktio).

Osatyössä II kaikkien psyykelääkkeiden esiintyvyys väheni merkitsevästi vanhainkodeissa (81-61%), kun taas tehostetussa palveluasumisessa ei tapahtunut samanlaista muutosta (65-64%). Opioidien käyttö kasvoi merkitsevästi molemmissa kohorteissa. Muistisairaat käyttivät vähemmän psyykelääkkeitä ja opioideja verrattuna ei-muistisairaisiin molemmissa kohorteissa.

Johtopäätökset: Neuropsykiatriset oireet ovat riskitekijä kaatumisille. Kaatumisriski kasvaa neuropsykiatristen oireiden lisääntyessä. Neuropsykiatristen oireiden arviointi tulisi ottaa osaksi kokonaisvaltaista arviota, kun pitkäaikaishoidossa asuvien ihmisen kaatumisriskiä halutaan pienentää. Liikuntaharjoittelu voi vähentää neuropsykiatrisiin oireisiin yhdistyvää kaatumisriskiä. Sekä neuropsykiatristen oireiden että muistisairauden vaikeusaste vaikuttaa terveyteen liittyvään elämänlaatuun. Neuropsykiatristen oireiden ja terveyteen liittyvän elämänlaadun yhteys on erilainen eri muistisairauden vaiheissa. Psyykelääkkeiden käytön esiintyvyys on vähentynyt viimeisen 14 vuoden aikana vanhainkodeissa Helsingissä, mutta samalla opioidien käyttö on lisääntynyt, johtaen siihen, että keskushermostoon vaikuttavia väsyttäviä lääkkeitä käytetään yhä paljon pitkäaikaishoidossa.

1 INTRODUCTION

As the world's population is aging at an increasing rate, the number of people with dementia is growing. Every year, there are almost 10 million new cases globally, one every three seconds. The total number of people with dementia is predicted to reach 82 million in 2030 and 152 million in 2050 (WHO, 2019).

Cognitive decline is considered the hallmark of dementia, but neuropsychiatric symptoms (NPSs) affect up to 97% of those diagnosed with dementia during the course of their illness (Steinberg et al. 2008). Clinically significant NPSs can result in various negative consequences, such as distress and decreased quality of life in both caregivers and patients, increased healthcare costs and early admission to long-term care (Beeri et al. 2002, Wancata et al. 2003, Lethin et al. 2017). NPSs are also related to psychotropic drug use (Selbæk et al. 2007, Wetzels et al. 2011) and lately its relationship with other central nervous system (CNS) drugs such as opioids has been under discussion (Brown et al. 2015, Kales et al. 2019).

People with dementia have a significantly higher risk of falling than those without (van Doorn et al. 2003). The risk is twice as high in community-dwelling people with dementia than in those without (Welmerink et al. 2010). The risk factors of falls are multiple and vary between community- and institution-dwelling older adults with dementia. Use of psychotropic drugs and dementia have both been shown to increase fall risk (Allan et al. 2009, Kröpelin et al. 2013, Fernando et al. 2017). In addition, there are some studies suggesting that NPSs are associated with falls (Sylliaas et al. 2012).

Earlier studies have thus shown that the prevalence of NPSs, falls and psychotropic drug use is very common in dementia, especially among those in long-term care (Rubenstein et al. 2006, Gulla et al. 2016). Less is known about the interplay of these factors. Therefore, the focus of this thesis is to understand the relationships between dementia, neuropsychiatric symptoms, falls and psychotropic drug use, and how they affect quality of life.

2 REVIEW OF THE LITERATURE

2.1 NEUROPSYCHIATRIC SYMPTOMS (NPSs) IN DEMENTIA

Dementia is characterized not only by cognitive and functional decline, but also by symptoms that affect an individual`s personality, emotions, and behavior (McKhann et al. 2011, Gitlin et al. 2012). These symptoms are called neuropsychiatric symptoms (NPSs) or behavioral and psychological symptoms of dementia (BPSD) (Finkel et al. 1996, Gilmore-Bykovskyi et al. 2019). In this thesis the term NPSs will be used. The impairment in cognitive function is sometimes preceded by NPSs causing confusion in the patient or his/her family long before dementia diagnosis is made (Taragano et al. 2009). Additionally, NPSs can be the most significant challenge in dementia care, for both clinicians and caregivers. Clinically significant NPSs may result in various negative consequences, such as distress and decreased quality of life in both caregivers and patients, early admission to long-term care, misuse of medication, and increased healthcare costs (Beeri et al. 2002, Wancata et al. 2003, Kales et al. 2005, Lethin et al. 2017). A broader understanding of NPSs is needed to improve their management.

2.1.1 EPIDEMIOLOGY OF NPSs

Almost all individuals with dementia experience at least one significant NPS during the course of their disease (Steinberg et al. 2008, Savva et al. 2009, Kales et al. 2015,) Sometimes it can be the first symptom of a neurocognitive disorder (NCD), but NPSs are most common in moderate–severe dementia (Cummings 1997, Zhao et al. 2016, Gallagher et al. 2017). A new term, “mild behavioral impairment” (MBI) has been suggested to describe a potential manifestation of prodromal dementia, similar to mild cognitive impairment (MCI), in which the cognitive deficits do not interfere with the capacity for

independence in everyday life (APA 2013, Ismail et al. 2016). MBI criteria have been proposed by the International Society to Advance Alzheimer's Research and Treatment. These criteria include changes in behavior or personality observed by the patient, informant, or clinician starting in later life (age≥50 years) and persisting at least intermittently for a minimum of six months. According to Ismael et al. affective and emotional dysregulation are common in preclinical dementia syndromes, often being predictors of neurodegenerative change and progressive cognitive decline (Ismail et al. 2018).

Neuropsychiatric symptoms include apathy, agitation, aggression, anxiety, depression, delusions, hallucinations, eating disorders and sleep impairment (Lyketsos et al. 2002). The most common and widely used tool to evaluate NPSs is the Neuropsychiatric Inventory (NPI) (Cummings 1997). Its properties are discussed in more detail in section 4.4.1. Other tools used to evaluate NPSs include the Cohen-Mansfield Agitation Inventory (CMAI), the Behavioral Pathology in Alzheimer's Disease rating scale (BEHAVE-AD), the Brief Psychiatric Rating Scale (BPRS), the Geriatric Depression Scale (GDS) and the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al. 1988).

NPSs form clusters, and four neuropsychiatric subsyndromes: hyperactivity, psychosis, affective symptoms, and apathy, have been identified (Aalten et al. 2007) (Figure 1).

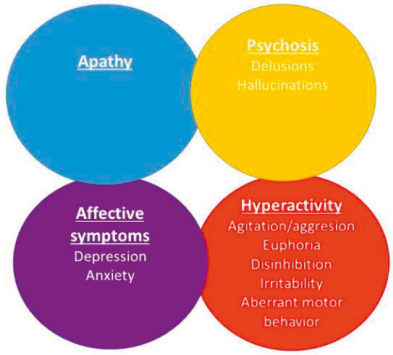


Figure 1. Neuropsychiatric subsyndromes in dementia (Aalten et al. 2007).

In a report from the European Alzheimer Disease Consortium the most common subsyndrome was apathy, followed by affective symptoms (Aalten et al. 2008). In a review by Zhao et al., apathy (49%) and depression (42%) were also the most common NPSs, followed by aggression (40%), anxiety (39%) and sleep impairment (39%). The less prevalent NPSs were disinhibition (17%), hallucinations (16%) and euphoria (7%) (Zhao et al. 2016). People with dementia are vulnerable to delirium, in which NPSs such as hallucinations and delusions may be prominent (Inouye et al. 2014). In differential diagnostics, possible underlying delirium should be considered, as symptoms of delirium and multiple NPSs have been shown to be highly overlapping (Hölttä et al. 2011).

Neuropsychiatric symptoms have been reported to be very common among both community-dwelling people with dementia as well as among long-term-care residents. According to the Cardiovascular Health Study, 75% of dementia participants exhibited NPSs (Lyketsos et al. 2002). According to the results of various studies, the prevalence is 82–92% in long-term care settings (Pitkälä et al. 2004, Selbæk et al. 2013, Björk et al. 2016). Several longitudinal studies have revealed NPSs to be persistent, even though individual symptoms can vary over time (Wetzels et al. 2010, Selbæk et al. 2014, Connors et al. 2018, and Helvik et al. 2018).

2.1.2 RISK FACTORS AND ASSOCIATIONS WITH NPSs

Many factors have been found to be associated with the development of NPSs. According to a review published in 2017 each NPS can have its own set of specific determinants, but a number of determinants are common across several symptoms (Kolanowski et al. 2017). Common NPS risk factors are often divided into environmental factors, caregiver factors and patient factors (Kales et al. 2015) (Figure 2).

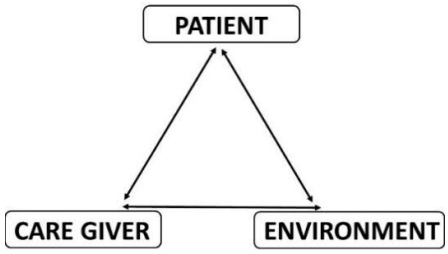


Figure 2. Three domains affecting the risk factors of NPSs (Kales et al. 2015)

Environmental factors encompass overstimulation and under-stimulation, lack of activity and structure, and lack of established routines. When considering caregiver factors, it is important to take into account communication issues, lack of knowledge and education about dementia and NPSs, stress, burden and possible caregiver depression (Feast et al. 2016, Gerlach et al. 2018). Environmental and caregiver factors may trigger NPSs independently or in interaction with brain-circuit disruptions caused by neurodegeneration (Kales et al. 2015). Patient factors cover a variety of factors such as unmet needs, pain, fear, frustration, insecurity, hunger, acute medical problems and premorbid personality or psychiatric disorders (Cohen-Mansfield et al. 2015, Kales et. al 2015). It has also been proposed that instead of being single events, NPSs are sequential, random, patterned clusters of behavior, which can recur repeatedly in the same person, thus bringing problems to symptom measurement, and evaluation of interventions (Connors et al. 2018, Woods et al. 2018).

It has been argued that the disruption in brain circuitry caused by underlying dementia leads to vulnerability to stressors and consequently to NPSs (Gerlach et al. 2018). In addition to large-scale networks, brain volume has also been shown to predict NPSs in Alzheimer's disease (AD), with frontal lobe volume being the strongest predictor (Boublay et al. 2020). Various dementia subtypes have been argued to have their own characteristic neuropsychiatric profiles (Cummings 1997), but not all investigators have reached this conclusion (Aalten et al. 2008). Compared with Parkinson's dementia,

according to Aarsland (2001), aberrant motor behavior, agitation, apathy, disinhibition, euphoria and irritability can be more severe in AD, while patients with Parkinson's dementia seem to have more hallucinations (Aarsland et al. 2001). Compared with AD, people with frontotemporal dementia can exhibit significantly more apathy, disinhibition and euphoria (Levy et al. 2007). Patients with vascular dementia may be more likely to have depression, and patients with dementia with Lewy bodies (DLB) have been found more often to exhibit delusions and hallucinations than patients with AD (Cummings 1997, Levy et al. 2007). A recent study also concerned the association between cerebrospinal fluid (CSF) biomarkers and NPSs in cases of AD. Lower levels of CSF amyloid-beta peptide-42 (Aβ42), higher levels of tau protein and p-tau (phosphorylated tau) were associated with presence of anxiety. Lower levels of CSF Aβ42 and smaller hippocampal volumes were associated with the presence of apathy. All associations were mediated by cognitive functioning (Banning et al. 2020).

Neuropsychiatric symptoms have been associated with the severity of cognitive impairment and declining functional abilities (Cummings 1997, Kolanowski et al. 2017). Several studies have shown that having NPSs impairs quality of life in both community-dwelling and institutionalized older adults with dementia (Hurt et al. 2008, Wetzels et al. 2010, Karttunen et al. 2011, Mjørud et al. 2014, Conde-Sala et al. 2016, Klapwijk et al. 2016, Hongisto et al. 2018). However, most of these studies have been conducted among people with mild or moderate dementia and the generalizability of the results among older adults with severe dementia can be questioned.

2.1.3 NON-PHARMACOLOGICAL TREATMENT OF NPSs

Non-pharmacological strategies are recommended as first-line treatment of NPSs (Kales et al. 2019). They have been studied extensively, as there have been more than 150 trials exploring their efficacy (Abraha et al. 2017, Dyer et

al. 2018, Hölttä et al. 2019) (Table 1. Evidence of the effects of non-pharmacological interventions in the treatment of neuropsychiatric symptoms of dementia). Unfortunately, there are several limitations when considering the evidence of efficacy, and implementation of non-pharmacological interventions. One example is the challenge of comparing different non-pharmacological treatment strategies. The majority of the studies have shown great variation in how the same type of intervention has been defined and applied. In addition, the populations, measures, follow-up duration and types of outcome have varied.

According to the best evidence available, behavioral management techniques, caregiver-based interventions or staff training in communication skills, person-centered care or dementia care mapping, and music-based therapies have been found to be the most effective treatment options (Abraha et al. 2017, Dyer et al. 2018, Hölttä et al. 2019). One of the most widely used approaches is the DICE approach (Kales et al. 2014). DICE is short for Describe, Investigate, Create and Evaluate. Another model is TIME (Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms) (Lichtwarck et al. 2018). Both models use a structured interdisciplinary biopsychosocial approach that consists of making a comprehensive assessment of underlying causes of neuropsychiatric symptoms and an individually tailored treatment plan.

There is no positive evidence concerning the use of cognitive training, cognitive stimulation, massage therapy, light therapy, aromatherapy, sensory garden or horticultural activities (Viggo Hansen et al. 2006, Chung et al. 2002, Woods et al. 2012, Forbes et al. 2014, Forrester et al. 2014, Gonzalez et al. 2014, Bahar-Fuchs et al. 2019). Data on the effectiveness of validation, reminiscence therapy, simulated presence and therapeutic design is inconsistent (Abraha et al. 2017, Woods et al. 2018). There is some preliminary evidence concerning the use of animal therapy and pet robot therapy, but the quality of evidence is poor and it comes from small trials (Lai et al. 2019, Leng

et al. 2019). An additional challenge in all non-pharmacological trials is in achieving blinding of participants and personnel.

The effectiveness of exercise on NPSs has also been studied, but the results are somewhat contradictory (Barreto et al. 2015, Forbes, et al. 2015, Öhman et. al 2017). This could be due to the fact that NPSs have mostly been studied in trials in which NPSs have been a secondary endpoint; thus Neuropsychiatric Inventory (NPI) points at baseline have been relatively low, creating a possible floor effect.

The international Delphi consensus process agreed in 2019 on DICE and music therapy as the most promising non-pharmacologic treatment approaches for overall NPSs and agitation (Kales et al. 2019). A stepwise approach to the management of NPSs was also suggested.

Table 1. Evidence of the effects of non-pharmacological interventions in the treatment of neuropsychiatric symptoms of dementia.

Intervention	Systematic Review/Study	Trials & participants	Measures	Results	Comments
Caregiver training, support and guidance	Livingston et al. 2005 Brodaty et al. 2012	7 RCTs, n=637 23 RCTs, n=3279	NPSs, agitation, depression	25/30 RCT's showed benefit In 25 RCTs NPSs were reduced, in 4 the results were neutral and in one negative. There was a significant reduction in the frequency of challenging behaviors at post-intervention	Effect size of 0.34, comparable to pharmacological treatment of NPSs No adverse effects
Exercise alone or with other interventions	Barreto et al. 2015 Forbes et al. 2015 Öhman et al. 2017	18 RCTs, 13 RCTs 1 RCT, n=140	Sleep, depression, agitation, NPSs	Exercise did not reduce global levels of NPSs (18 RCTs). Exercise significantly reduced depression levels (7 RCTs)	Most of the exercise interventions were not planned to reduce NPSs. NPSs were often a secondary outcome; thus NPI points at baseline were relatively low, creating a floor effect
Multi-component, tailored, individual interventions	Olazarán et al. 2010 Moniz-Cook et al. 2012	12 RCTs, n=2300	NPSs	In 9 RCTs NPSs were reduced and 3 RCTs were neutral	Effect size on NPSs similar or higher than the effect obtained by drugs, 0.57–0.60; for mood lower, 0.37
Music-based therapeutic interventions	Chang et al. 2015 van der Steen et al. 2018	10 RCTs 22 RCTs, n=1097	NPSs, anxiety, depression, agitation, aggression	Moderate to high effect on improving disruptive behaviors, a moderate effect on reducing anxiety and depression. Reduction in depression and overall behavior problems, but no decrease in agitation or aggression	A larger and more positive effect on patients with mild to moderate dementia than on patients with moderate to severe dementia. Minimum amount of sessions to obtain positive results was five
Cognitive training	Bahar-Fuchs et al. 2019	8 RCTs, n=577	Mood	Cognitive training did not reduce NPSs or improve mood	Moderate-quality evidence from one trial showed improved mood of the caregiver
Cognitive stimulation	Woods et al. 2012	15 RCTs, n=718	Mood	Cognitive stimulation did not reduce NPSs or improve mood	Most of the studies were of low quality and the sample sizes of the studies were not powered to detect statistically significant effects

Table 1. Continued…

Intervention	Systematic Review/Study	Trials & participants	Measures	Results	Comments
Massage therapy	Viggo Hansen et al. 2006	2 RCTs, n=110	Agitation	Low-quality evidence for immediate or short-term reduction of agitation	Evidence so limited that it is not possible to draw general conclusions about benefits
Light therapy	Forbes et al. 2014	13 RCTs, n=499	NPSs, mood	No effect of light therapy on sleep, agitation, or NPSs	Insufficient numbers of trials to conduct subgroup analyses on modality of light therapy, time of day, intensity and duration
Aromatherapy	Forrester et al. 2014	7 RCTs, n=428	NPSs, agitation	One study (Burns 2011) showed no significant difference in treatment effect, while another study (Ballard 2002) showed improvement in agitation	Quality of evidence very low. Several methodological difficulties in the studies
Snoezelen and Horticultural activities	Chung et al. 2002 Gonzalez et al. 2014	2 RCTs, 16 n=175 16 studies, n=549 (2 case studies, 1 survey, 11 intervention studies, 2 RTCs)	Behavior and mood Agitation, CMAI wandering, sleep	No significant short-term or long-term effect on behavior or mood Tendency to improved sleep, and less agitation	No meta-analyses because of the limited number of trials and different study methods in the available trials The small samples sizes and the lack of RCTs made it difficult to draw conclusions about causal relationships
Animal-assisted therapy	Lai et al. 2019	5 RCTs, n=225	NPSs, agitation, mood	Slight reduction in depressive symptoms, no effect on NPSs or agitation	Small sample sizes, diversity of outcomes and outcome measures
Pet robot interventions (PARO)	Leng et al. 2019	6 RTCs, n=502	NPSs, agitation, mood	Reduction in depressive symptoms and agitation	No effect on quality of life. Quality of evidence low to moderate

RCT = randomized controlled trial; CMAI = Cohen-Mansfield Agitation Inventory

2.1.4 PHARMACOLOGICAL TREATMENT OF NPSs

Non-pharmacological treatment options are always the primary treatment options for NPSs, because of the small effect sizes and the possible harmful effects of pharmacological treatment (Sink et al. 2005, Kales et al. 2019) (Table 2. Evidence of the effects of pharmacological treatment of neuropsychiatric symptoms of dementia). Despite this, pharmacological treatment is still widely used. Such treatments are based on the neurobiological theoretical framework in which NPSs result from synaptic or circuit disconnections in various brain networks (Kales et al. 2015).

Pharmacological treatment may be considered only after significant efforts have been made using non-pharmacological treatment. Treatment should be used specifically in three specific scenarios, which may be more prone to efficacy of drug treatment: major depressive disorder with or without suicidal ideation, psychosis causing harm or potential for harm, and aggression with risk to self or others (Kales et al. 2014). Pharmacological treatment options consist of use of cognitive enhancers or psychotropics, which include antipsychotics, antidepressants, anxiolytics, hypnotics and sedatives. Other CNS drugs such as anticonvulsants and opioids have also been studied. Current Care Guidelines in Finland recommend cognitive enhancers as first-line drug treatment for NPSs (Memory Disorders: Current Care Guidelines, 2017).

The drugs of choice should be targeted to specific symptoms (Figure 3). Close attention should be paid to the evidence of medication efficacy in relation to specific symptoms, and the overall risks associated with untreated symptoms compared with those connected to the medication.

When medication is initiated for NPSs, the persistence of symptoms should be assessed thoroughly to determine if patients benefit from continued medication versus drug discontinuation, while taking into account the possibility of symptomatic relapse and possible subsequent decline (Phan et al. 2019). In the United States no drugs have been approved by the Food and Drug Administration for the treatment of NPSs. In Finland, however, risperidone is approved for symptomatic management of severe NPSs (Memory Disorders: Current Care Guidelines, 2017).

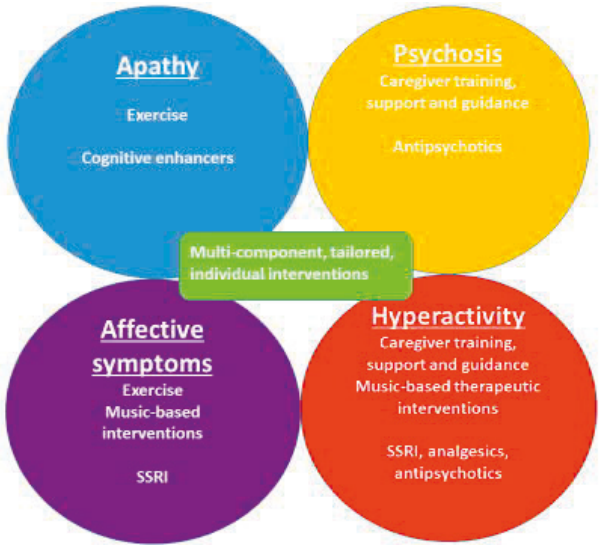


Figure 3. Non-pharmacological and pharmacological treatments used for different neuropsychiatric subsyndromes (modified from Kales et al. 2015, Kales et al. 2019, Hölttä and Pitkälä 2019). SSRI = serotonin selective reuptake inhibitor.

Table 2. Evidence of the effects of pharmacological treatment of neuropsychiatric symptoms of dementia

Medication	Study/review	Trials & participants	Measures	Results	Side effects	Comments
Cholinesterase inhibitors (ChEIs)	Birks 2006 Birks 2018 Tricco et al. 2018	3 RCTs, n=1003 4 RCTs, n=1035 26 RCTs, n=5138	NPI NPI NPI	ChEIs reduced NPSs measured by NPI. Donepezil reduced NPSs measured by NPI, but the result was not statistically significant. ChEIs alone and in combination with memantine reduced NPSs	Nausea, vomiting, diarrhea, headache, bradycardia, falls, anorexia As above + dizziness, constipation, hypertension	Median difference in NPI points -2.44, (95% CI -4.12 to -0.76) Mean score in the intervention group was -1.62 points (95% CI -3.43 to 0.19, p = 0.08) Donepezil -1.32 points (95% CI -2.60 to 0.09), Donepezil + Memantine -5.23 (95% CI -8.72 to -1.56). Short follow-up, mean 27 weeks.
Memantine	Kishi et al. 2017 McShane et al. 2019	11 RCTs, n= 3298 14 RCTs, n=3674	NPI NPI, CMAI, BEHAVE-AD	Small benefit for NPSs, in aggression and disinhibition. Memantine seemed to reduce NPSs in moderate to severe AD	Dizziness, constipation, hypertension	Small effect size, in all patients MD -0.16 (95% CI -0.29 to -0.04), in moderate-severe AD MD -0.20 (95% CI -0.34 to -0.07) Improvement in NPI points MD 1.84 (95% CI 1.05 to 2.76)
Atypical antipsychotics	Ballard et al. 2006	16 RCTs, n=5574	CMAI, BEHAVE-AD, NPI-NH	Benefit of olanzapine for aggression and risperidone for aggression and psychotic symptoms	Stroke (OR 3.9), falls, extrapyramidal symptoms	This review concerned risperidone, olanzapine and aripiprazole.
Antidepressants	Dudas et al. 2018	8 RCTs, n=614	Hamilton Depression Rating Scale, Cornell Scale for Depression GDS	Little difference on depression symptom rating scales between the antidepressant- and placebo-treated groups after 6 to 13 weeks	Falls, hyponatremia, dry mouth	Subgroup analyses on SSRIs, venlafaxine, mirtazapine, and TCAs separately. No significant differences between these subgroups

Table 2. Continued…

Medication	Study/review	Trials & participants	Measures	Results	Side effects	Comments
Anxiolytics and sedatives	Tampi et al. 2014	5 RCTs, n=498	Every study used different measures	No significant difference in efficacy between the drugs	Sedation, falls	No placebo-controlled studies. Efficacy compared with old antipsychotics. Short-term trials from 24 hours to 8 weeks.
Hypnotics	McCleery et al. 2016	4 RCTs, n=222 melatonin 1 RCT, n=30 trazodone	Sleep time, nocturnal awakenings	No benefit from melatonin on sleep time or awakenings. Trazodone increased sleep time an average of 43 min	Melatonin: no serious side effects were reported. No differences in Side effects between the groups	Small study samples. Almost all had moderate to severe dementia. Two-week RCT, only 15 patients with AD taking trazodone, mean MMSE score 11.
Anticonvulsants	Seitz et al. 2013 Baillon et al. 2018	4 RCTs, n=361 5 RCTs, n=430	BPRS, NPI-NH BPRS, CMAI	Carbamazepine was associated with a reduction in agitation and aggressiveness. No beneficial effect of valproate on NPSs	Somnolence, hyponatremia	Old studies, small sample sizes. E.g. carbamazepine study in 1998, 55 participants from nursing homes.
Pain medication Opioids	Husebø et al. 2011	1 RCT, n=352	CMAI, NPI-NH	Stepwise protocol of pain treatment reduced agitation	Falls, sedation, constipation	Stepwise protocol included paracetamol, morphine, buprenorphine transdermal patch, or pregabalin.

BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale; CMAI = Cohen-Mansfield Agitation Index; BPRS = Brief Psychiatric Rating Scale; NPI-NH = Neuropsychiatric Inventory Nursing Home version ; GDS = Geriatric Depression Scale; OR = odds ratio; MD = mean deviation; TCAs = tricyclic antidepressants; MMSE = Mini-Mental State Examination

2.1.4.1 Cognitive enhancers

Cognitive enhancers such as cholinesterase inhibitors (ChEIs) and memantine are used in primary treatment of the cognitive symptoms of Alzheimer's disease, but the results of a systematic review and a meta-analysis have suggested that such types of medication may also help to alleviate NPSs (Trinh et al. 2003, Birks 2006). In Finland cognitive enhancers are seen as part of the first-line pharmacological treatment of NPS (Memory Disorders: Current Care Guidelines, 2017). Recent study findings on their effectiveness are somewhat contradictory. In 2018 a Cochrane review showed no significant difference between donepezil and placebo as regards behavioral symptoms measured by the NPI (Birks et al. 2018), but the combination of donepezil and memantine was found to significantly improve behavior versus placebo (Tricco el al. 2018). A recent Cochrane systematic review also revealed strong evidence that memantine has a small beneficial effect on mood and behavior (McShane et al. 2019). These results must be interpreted with caution, because they are based on clinical trials of relatively short duration, and NPSs tend to fluctuate with time.

2.1.4.2 Antipsychotic medication

One of the most commonly used classes of drugs for pharmacological treatment of NPSs is the class of antipsychotics (Olsson et al. 2010, Janus et al. 2016). They also have the strongest evidence base (Kales et al. 2015). However, the treatment effects are small, effect sizes being 0.13–0.16, and are mainly seen in reducing aggressive behavior and psychotic symptoms (Kales et al. 2015). According to a Cochrane review, risperidone and olanzapine are useful in reducing aggression, and risperidone in alleviating psychosis, but both are associated with serious risks of adverse effects, such as death, cerebrovascular events and extrapyramidal symptoms (Schneider et al. 2005,

Ballard et al. 2006). Other possible side effects include cognitive decline, somnolence, orthostatic hypotension, abnormal gait, falls, QT prolongation and metabolic effects such as weight gain, dyslipidemia and diabetes (Schneider et al. 2006).

A Cochrane review published in 2018 suggests that antipsychotics may be successfully discontinued in older people with dementia and NPSs who have been taking antipsychotics for at least three months. The authors found that discontinuation may have little or no important effect on behavioral and psychological symptoms (Van Leeuwen et al. 2018). This is consistent with the observation that most NPSs in dementia are intermittent and often do not persist for longer than three months. Based on the trials in this review, there is still uncertainty as to whether or not discontinuation of antipsychotics leads to a decrease in excess mortality. The balance of possible harms and benefits of antipsychotic drug use for the treatment of NPSs must be individually assessed. People with psychosis, aggression or agitation who responded well to long-term antipsychotic drug use, or those with more severe NPSs at baseline, may benefit behaviorally from continuation of antipsychotics, whereas discontinuation may reduce agitation among people with mild NPSs at baseline (Van Leeuwen et al. 2018). However, these conclusions are based on only a few studies and small subgroups. Further evidence of benefits and harms associated with withdrawal of antipsychotic medication is required (Van Leeuwen et al. 2018).

2.1.4.3 Antidepressant medication

Another commonly used class of drugs for the treatment of NPSs is the class of antidepressant drugs. According to a Cochrane review published in 2018, available evidence does not provide strong support for the efficacy of antidepressants for treating depression in dementia, especially beyond 12 weeks (Dudas et al. 2018). The evidence on remission rates favored antidepressants but it was of moderate quality. Antidepressant medication,

especially selective serotonin reuptake inhibitors (SSRIs), may have efficacy for treating agitation, but the possible cognitive and cardiac adverse effects may limit its application (Seitz et al. 2011, Porsteinsson et al. 2014). There is evidence that antidepressant treatment may cause adverse events such as falls, sleep changes, nausea, vomiting, hyponatremia and QT prolongation (Hartikainen et al. 2007, Porsteinsson et al. 2014, Dudas et al. 2018, Seppälä et al. 2019). According to the latest Beers criteria, tricyclic antidepressants (TCAs) and other drugs with significant anticholinergic effects, such as paroxetine, should be particularly avoided (Fick et al. 2019). Low-dose mirtazapine is often used off-label for sleep problems in dementia, but there is no data supporting this action (McCleery et al. 2014).

2.1.4.4 Anxiolytics and hypnotics

While sleep disorders are a common complaint in patients with dementia, with > 50% of patients affected at the more severe stages of the disease (Kazui et al. 2016), there is a lack of evidence on the use of anxiolytics and hypnotics in people with dementia. In particular, there are no RCTs of drugs that are widely prescribed for sleep problems in dementia, including the benzodiazepine and non-benzodiazepine hypnotics (McCleery et al. 2016). There is considerable uncertainty about the balance of benefits and risks associated with these common treatments. Benzodiazepines constitute one of the main risk factors of falls and fractures in older people. They seem to be associated with an increased risk of falls not only in long-term use but also after a new prescription (Hartikainen et al. 2007). A Cohrane review published in 2016 showed no evidence that melatonin (up to 10 mg) helped sleep problems in patients with moderate to severe dementia due to AD (McCleery et al. 2016). NICE guidelines for dementia do not recommend melatonin for people with dementia (NICE, 2018). There is some evidence to support the use of a low dose (50 mg) of trazodone, but the evidence is weak, and trazodone seems to be no safer than benzodiazepines as regards falls (Bronskill et al. 2018). There is no evidence of any effect of ramelteon on sleep in patients with dementia (McCleery et al. 2016).

2.1.4.5 Other drugs for NPSs

Available studies carried out to evaluate the use of anticonvulsants such as valproic acid, carbamazepine, pregabalin and gabapentin have not shown clear evidence of benefit and they are associated with increased risks of adverse effects and mortality (Kim et al. 2008, Konovalov et al. 2008). A Cochrane review published in 2018 supported earlier findings that valproate preparations are probably ineffective in treating agitation in people with dementia, and they are also associated with an elevated rate of adverse effects. On the basis of current evidence, valproate therapy cannot be recommended for management of agitation in dementia (Baillon et al. 2018).

Pain may be one cause of agitation in dementia. Many older people with dementia also have chronic, painful conditions. Pain may be experienced differently due to the dementia and may often go uncommunicated or untreated. It can be hard to know whether agitation is due to pain. In a cluster randomized trial in Norway a systematic approach to the management of pain significantly reduced agitation among long-term-care residents (Husebø et al. 2011). It has been hypothesized that opioids may be useful in the treatment of agitation, where pain is an underlying factor, but they may also be effective for relieving distress in the absence of physical pain. In a Cochrane review (2015) it was found that there is no high-quality evidence to determine whether opioids are a safe or effective treatment for agitation in dementia (Brown et al. 2015). Compared with nonuse, long-term opioid therapy is associated with increased risks of abuse, overdose, falls and fractures, with several studies showing dose-dependent associations (Chou et al. 2015, Seppälä et al. 2018). Opioid use has also been associated with cognitive decline (Wright et al. 2009).

2.1.4.6 Temporal trends in the use of psychotropics

Based on the results of various studies reporting serious adverse effects of psychotropic drug use for the treatment of NPSs, a reduction of inappropriate use has been of interest as regards governmental policies. As early as in 1987, OBRA (Omnibus Budget Reconciliation Act) in the United States recommended reducing the use of psychotropic drugs. Antipsychotic drug use in US nursing homes (NHs) declined after implementation of this regulation, whereas the use of antidepressants increased between 1996 and 2006 (Garrard et al. 1995, Hanlon et al. 2010). The latest report (2020) shows an increase in the use of psychotropics, as the percentages of NH residents in the US receiving anxiolytics, antidepressants, and antipsychotics in 1995 were 15%, 20%, and 16%, respectively, and by 2015 these figures had increased to 23%, 49% and 20% (Fashaw et al. 2020).

In 2012, to address the high level of use of antipsychotics in older adults with dementia in US nursing-home settings, the Centers for Medicare & Medicaid Services (CMS) launched the National Partnership to Improve Dementia Care in Nursing in order to improve the quality of care for nursing-home residents with dementia, primarily by reducing antipsychotic use. The program led to a significant reduction in antipsychotic use from 24% in 2011 to 14.3% in 2019 (CMS, 2020). Unfortunately, there are indications of compensatory increases in the use of other sedating psychotropics, not measured by the CMS, as well as mood stabilizers (Maust et al. 2018). Thus, measuring only the use of antipsychotics may be an inadequate proxy for quality of care and may contribute to a shift in prescribing alternative types of medication such as opioids and antiepileptics, with an even poorer risk-benefit balance (Maust et al. 2018, Kales et al 2019). This case serves as an important reminder to look at the big picture and not just a single piece of the puzzle.

In Finland, the prevalence of psychotropic drug use has been reported to be higher in community-dwelling people with AD compared with people without

AD (Taipale et al. 2014). According to a 2018 study, the prevalence of psychotropic medication five years after AD diagnosis was 49.9% in people with AD compared with 25.9% in people without AD (Orsel et al. 2018.). A recent Swedish study revealed that AD patients who used ChEIs had a lower risk of antipsychotic and anxiolytic use initiation (Tan et al. 2020). The prevalence of psychotropic drug use in Europe and Australia is more common in long-term-care residents, varying between 52–80% in nursing homes and 53–68% in assisted-living facilities, according to the results of various studies (Hosia-Randell et al. 2005, Selbæk et al. 2007, Stafford et al. 2011, Richter et al. 2012, Rolland et al. 2012, Pitkälä et al. 2015, Helvik et al. 2017).

Given concerns about changing trends in CNS and psychotropic medication use globally, and the many factors that influence their use, a current assessment of psychotropic medication use in Finnish long-term care settings is required.

2.2 DEMENTIA

To obtain a better understanding of NPSs in dementia, it is important to fully understand underlying dementia. Dementia is defined as a syndrome in which there is deterioration in cognitive function beyond what might be expected from normal ageing (WHO, 2019). The core criteria also require that there is a decline from a previous level of functioning and that symptoms significantly interfere with the ability to function when carrying out usual activities (McKhann et al. 2012).

According to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification, neurocognitive disorders are divided into major NCDs, minor NCDs and delirium (APA, 2013). Dementia is included under major NCDs and is in turn divided into Alzheimer's disease (AD), vascular dementia (VAD), Dementia with Lewy bodies (DLB), Parkinson´s

disease dementia (PDD), frontotemporal dementia (FTD) and alcohol-related dementia.

Other widely used criteria include those of ICD-10 (WHO 1993) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) criteria for AD (McKhann et al. 2011). The core features of dementia in all criteria include significant cognitive decline from a previous level and its interference with daily functioning. In addition, all criteria include NPSs as an additional qualifying feature. NINCDS-ARDRA criteria to diagnose AD are used in both clinical practice and research. These criteria were last revised in 2011 (McKhann et al. 2011). In clinical work the most often used diagnostic criteria for AD at present are those of the International Classification of Diseases, 10th edition (ICD-10) (WHO, 1993). Its latest edition (ICD-11) was released in May 2019, but it is not yet in clinical use. The manual DSM-5 is commonly employed in mental-health research (APA 2013).

The term 'dementia' originates from the Latin word 'demens', originally meaning 'madness' or being out of one's mind. The use of the word dementia has been questioned, as the term can be seen as pejorative and stigmatizing (Trachtenberg et al. 2008). It has been suggested that it would be better to simply refer to each neurocognitive disorder as a specific disease (e.g. AD, VCI or FTLD etc.), which could be seen as a logical resolution to the terminology problem (Jellinger et al. 2010). When a general term is needed, then neurocognitive disorder could be a clear, truthful, and nonpejorative option. In DSM-5 the term dementia has been replaced with "major and mild NCD" in an effort to reduce the stigma attached to the term dementia (APA, 2013). In Finland, in the Current Care Guidelines, the term "memory disorder" is used instead of dementia (Memory Disorders: Current Care Guidelines, 2017). In addition, the phrase "dementia-friendly" was replaced by "memory-friendly" when in the National Memory Programme 2012–2020 "Creating a memory-friendly Finland" was established (Finnish Ministry of Social Affairs and Health, 2013). Globally, however, the word "dementia" is still very much used

in clinical practice and in a research context. For this reason, as a general term the word “dementia” will be used in this thesis.

2.2.1 EPIDEMIOLOGY OF DEMENTIA

According to the World Health Organization (WHO) around 50 million people worldwide have dementia. Every year, there are almost 10 million new cases, one every three seconds. The total number of people with dementia is predicted to reach 82 million in 2030 and 152 million in 2050 (WHO, 2019). In Finland, approximately 190,000 people have a memory disease and there are approximately 14,500 new cases of dementia each year (Memory Disorders: Current Care Guidelines 2017). Thus, dementia constitutes an increasing challenge to healthcare systems worldwide (Nichols et al. 2016).

The worldwide age-standardized prevalence of dementia in the general population aged 60 and over at a given time is between 5–8% and it varies little between world regions (Prince et al. 2013). Alzheimer Europe compared the prevalence of dementia between the different European countries in 2013. The average prevalence rate for dementia in Europe was 1.55%. In Finland it was slightly higher, being 1.71%. The highest prevalence was in Italy, 2.09%. Slovakia, Ireland and Cyprus had the lowest rates of prevalence, 1.07–1.08% (Alzheimer Europe, 2013). These results should be interpreted with caution, as changes in the prevalence of dementia can be modulated by a complex combination of societal determinants affecting diagnostic processes, survival and lifestyle factors. Another factor to consider is that the prevalence rates are likely to be affected by increased attention to dementia and awareness of it, shifting diagnostic boundaries and the age structure of each population (Wu et al. 2016).

A growing number of studies have revealed a decline in the prevalence or incidence of dementia in Western countries (Matthews et al. 2013, Wu et al. 2017, Harrison et al. 2020). Even so, as the population is aging, the absolute

number of dementia cases will continue to grow despite the decreasing prevalence. The good news is that dementia morbidity seems to be on a down-turn, at least in high-income countries. In the Framingham Heart Study it was found that the age at dementia onset has increased on average by around 1.5 years, whereas years alive with dementia have decreased on average by one year over time (Dufouil et al. 2018). There are no data yet from low-income countries, where populations are aging most rapidly. As prevalence is a function of incidence and duration of survival with the disease, careful investigation into the trajectories of dementia are needed to ascertain service needs in the future (Ganguli et al. 2017).

2.2.2 RISK FACTORS OF DEMENTIA

Age is the strongest risk factor of cognitive decline, as both the incidence and the prevalence of dementia increase exponentially with increasing age (Corrada et al. 2010, Lucca et al. 2015). However, aging without dementia is possible (Qiu et al. 2018). The results of several recent studies have shown that lifestyle-related risk factors have a relationship with the development of dementia (Kivipelto et al. 2018, Ngandu et al. 2015, Lourida et al. 2019). These risk factors include physical inactivity, an unhealthy diet (such as low intake of fruits, vegetables and whole grains and high intake of saturated fats, sugar and salt), harmful use of alcohol or tobacco and a low level of education. In a recent study it was also suggested that more frequent social contact in middle-age years is associated with a lower dementia risk in older age (Sommerlad et al. 2019). The link from frequent social contact to a lower dementia risk could be a development of a higher cognitive reserve, although it is possible that the ability to maintain more social contact may be a marker of cognitive reserve itself.

Some chronic medical conditions are also associated with an increased risk of dementia, including hypertension, diabetes, hypercholesterolemia, obesity and depression (Livingston et al. 2017, Strandberg et al. 2019). With respect to genetic factors, APOE e4 is the strongest predictor of Alzheimer's disease

(Hersi et al. 2018). Also, groups of people on specific forms of medication, such as those on anticholinergic medication have been suggested to be at an increased risk of dementia (Coupland et al. 2019).

The existence of these potentially modifiable risk factors makes dementia prevention possible through a public-health approach, as the proactive management of modifiable risk factors has been shown to delay or slow down the onset or progression of the disease (Kivipelto et al. 2018). In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the largest completed trial so far, 1260 individuals aged 60–77 years with an increased dementia risk score were randomly assigned to receive multidomain lifestyle counselling including nutritional guidance, group and individual physical activity, cognitive training, and intensive monitoring of vascular and metabolic risk factors (n=631), or regular health advice (n=629) (Ngandu et al. 2015). At baseline, all participants were given oral and written information and advice on a healthy diet and physical, cognitive, and social activities beneficial for management of vascular risk factors and disability prevention. The intervention group additionally received four intervention components. Cognitive function improved significantly during the two years of intervention in both groups, but the intervention group improved significantly more than the control group. The challenge with the intervention is that it was long and very intensive, which makes it hard to replicate in the real world. Follow-up of the FINGER study is still ongoing. In time it will also show the effect of the intervention on the incidence of dementia. A CAIDE Dementia Risk Score App has been developed as an evidence-based mobile application to predict the risk of dementia (Kivipelto et al. 2006, Sindi et al. 2015). The App is meant to encourage users to actively decrease their modifiable risk factors and hence postpone cognitive impairment and dementia. A CAIDE score was used as an inclusion criterion in the FINGER study.

Other multidomain lifestyle interventions carried out in recent years include the French Multidomain Alzheimer Preventive Trial (MAPT) and the Dutch

Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial (Kivipelto et al. 2018). The primary outcomes were cognition measured by a composite score (MAPT), and dementia incidence (PreDIVA). Neither the MAPT nor the PreDIVA RCTs accomplished their primary endpoints, but they showed beneficial effects of intervention in specific subgroups of participants. The PreDIVA trial revealed a reduced risk of non-AD dementia in the intervention group. The MAPT trialists reported less decline in the intervention group in ten MMSE orientation items compared with the control group, but no difference in other cognitive outcomes was found. One explanation for these less than encouraging results could be the lower intensity of the intervention measures compared with those in the FINGER trial.

WHO Guidelines on reduction of risk of cognitive decline and dementia were published in May 2019 (WHO, 2019). These guidelines give recommendations concerning twelve different risk factors: low levels of physical activity, smoking, poor diet, alcohol misuse, insufficient or impaired cognitive reserve, lack of social activity, unhealthy weight gain, hypertension, diabetes, dyslipidemia, depression, and hearing loss.

2.2.3 DIAGNOSIS OF DEMENTIA

Timely and accurate diagnosis of any neurocognitive disorder is crucial as this enables correct treatment and a rehabilitation plan and will help families plan ahead (Dassel et al. 2019). A timely diagnosis can also reduce unnecessary suffering and increase family members' understanding of dementia and NPSs even though no disease-modifying treatment is yet available. On the other hand, overdiagnosis of dementia, such as identification of characteristic AD pathology, e.g. amyloid plaques in the brain (although these may never lead to dementia) can expose individuals to adverse effects and complications. This will also increase costs of diagnosis and treatment without the benefit of preventing a clinically significant disease (Langa et al. 2019). It is known from various studies that more than half of the individuals with MCI will not

progress to dementia (Canevelli et al. 2016, Ganguli et al. 2019, Shimada et al. 2019). Some will remain stable and some might even revert to normal cognition; thus they should not all be subjected to the same therapeutic strategies.

Especially in older populations, the diagnostic process can be complicated, as there are various other factors affecting cognition, such as poor vision, hearing and multimorbidity. These should always be taken into account when interpreting the diagnostic work-up. Differential diagnostics can also pose a challenge, especially when differentiating dementia with NPSs from delirium (Hölttä et al. 2011). Delirium reflects a rapid change in brain function with disturbances in arousal and attention, whereas dementia develops over time, with slow progression (Inouye et al.2014).

The most common progressive neurocognitive disorder leading to dementia is Alzheimer's disease (AD) (WHO, 2019). This is a neurodegenerative disorder currently assumed to be caused by amyloid plaques and neurofibrillary tangles accumulating in the brain (Perl, 2010). Studies published in the recent years have shown that AD seems to be an umbrella term including different types of disorder (Murray et al. 2011). The second most prevalent cause of dementia is vascular dementia (VAD), which can be caused by various types of vascular pathologies in the brain, such as “large vessel” (strategic infarctions or multi-infarct dementia) or “small vessel” (subcortical lacunar infarcts and white matter hyperintensities) disease (O’Brien et al. 2015). Especially in older age, symptoms and brain changes of different dementias often overlap. Mixed dementia caused by vascular cognitive impairment (VCI) and AD has emerged as the leading cause of age-related cognitive impairment (Iadecola 2013).

Other less frequent causes of dementia include frontotemporal lobar degeneration (FTLD), including the behavior variant frontotemporal dementia, and primary progressive aphasias, dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD). There are also several other diseases that can lead to dementia, such as normal pressure hydrocephalus

and Parkinson-plus syndromes such as multiple-system atrophy (MSA), progressive supranuclear palsy (PSP) and cortical-basal ganglionic degeneration (CBGD) (Memory Disorders: Current Care Guidelines, 2017). In the last five years two new disease entities have been recognized: a "limbic-predominant age-related TDP-43 encephalopathy" (LATE) and a "primary age-related tauopathy" (PART) (Crary et al. 2014, Nelson et al. 2019). Their clinical significance and relationship to AD is still under ongoing research.

2.2.4 MANAGEMENT OF DEMENTIA

Treatment of dementia depends on its cause. No disease-modifying treatment is available to date, but there are four drug treatments for AD that may temporarily improve the different symptoms caused by the disease (Galimberti et al. 2011). They are also widely used for controlling the NPSs of dementia.

Donepezil, rivastigmine, and galantamine are all cholinesterase inhibitors (ChEIs). They have been on the market for approximately 20 years, as donepezil was approved in 1997. They are considered to represent first-line pharmacotherapy for mild to moderate Alzheimer's disease and for the treatment of NPSs (Memory Disorders: Current Care Guidelines 2017, NICE 2018, Joe et al. 2019). They act by increasing the availability of acetylcholine in the extracellular space, which in turn promotes neuronal activity and cholinergic signaling in the brain (Francis et al. 1999). Cholinesterase inhibitors have been found to be effective in improving cognitive functioning in patients with mild to severe AD (Joe et al. 2019). However, the effect sizes found in clinical trials have been small to moderate (0.15–0.28, depending on the dose) (Rockwood 2004, Kaduszkiewicz et al. 2005, Birks 2006). Another limitation may be the generalizability of the data: many older people with dementia also have other comorbidities, excluding them from clinical trials.

Despite the small variations in the mode of action of the three ChEIs there is no evidence of any differences between them with respect to efficacy (Birks 2006). There seem to be some differences in adverse effects, with fewer adverse effects associated with donepezil compared with oral rivastigmine (Birks 2006, Birks et al. 2018). Donepezil is the most widely used ChEI in Finland, probably because of its relatively good tolerability and easier titration routine (Linna et al. 2019). Cholinesterase inhibitors are associated with possible gastrointestinal and cardiopulmonary side effects as well as dizziness, headache, insomnia, incontinence, and muscle cramps (Birks 2006, Tricco el al. 2018). Donepezil has been proved to be cost-effective (Birks et al. 2018).

The fourth drug approved for the treatment of AD is memantine, which is an NMDA (N-methyl-d-aspartate) receptor antagonist affecting glutamate metabolism and blocking the toxic effects of overactive glutamatergic activity (Johnson et al. 2006). The efficacy of memantine has been proved in cases of moderate-to-severe AD in monotherapy or in combination with a ChEI (Matsunaga et al. 2015, McShane et al. 2019). Possible side effects of memantine include headache and dizziness, but overall, memantine is better tolerated than the ChEIs (McShane et al. 2019).

The same medications that are used to treat AD are among the drugs prescribed to control symptoms of other types of dementia, such as LBD and PDD (Rolinski et al. 2012, Walker et al. 2015). The questionable efficacy of AD medication in cases of VAD, combined with concerns over possible adverse effects, has led to guidelines concluding that cholinesterase inhibitors and memantine should not be used in patients with pure VAD, but may be used in those with a combination of VAD and AD (Erkinjuntti et al. 2002, O'Brien et al. 2015, Birks et al. 2006, Birks et al. 2013).

As there have been no significant advances in the pharmacological treatment of dementia in recent years, the focus has moved more to non-pharmacological therapies. There is promising evidence that improvements brought about by way of non-pharmacological interventions are of similar effect size as with

pharmacological treatments but with fewer side effects. The most promising non-pharmacological treatments are multicomponent interventions including individual assessment, exercise, nutrition, case management and cognitive stimulation (Olazarán et al. 2010).

Available evidence suggests that exercise programs may maintain physical functioning and prevent falls in people with dementia (Pitkälä et al. 2013, Burton el al. 2015, Forbes et al. 2014). Tailored nutritional guidance has also been found to enhance nutrition and quality of life and to prevent falls among community-dwelling individuals with Alzheimer's disease (Suominen et al. 2015). Case management of elderly couples with dementia has been shown to lead to reduction in use and expenditure of municipal services (Eloniemi-Sulkava et al. 2009). Self-management group rehabilitation for persons with early dementia and their spouses has been shown to have beneficial effects on the health-related quality of life (HRQoL) of spouses and cognitive function among people with dementia, without increasing total costs (Laakkonen et al. 2016). There is also consistent evidence from various trials concerning the benefits of cognitive stimulation programs on cognition in people with mild to moderate dementia, although the quality of the evidence has been questioned, as the studies have had limited sample sizes and limited information on randomization (Woods et al. 2012).

Supporting evidence for the use of occupational therapy, complementary and alternative medicine, and new technologies, including information and communication technologies, assistive technology and domotics, virtual reality, gaming and telemedicine is still preliminary (Zucchella et al. 2018). According to the results of a 12-week RCT in Finland, systematic cognitive training did not have an effect on global cognition or HRQoL in community-living people with mild to moderate dementia (Kallio et al. 2018).

2.2.5 DEMENTIA IN LONG-TERM CARE

As dementia progresses it often leads to institutional care. In Finland, as in other Western countries, a large proportion of residents in institutional care have dementia. There were 54 411 older people in permanent institutional care (including nursing homes and assisted-living facilities) in Finland in 2018 (Finnish Institute for Health and Welfare, 2019). It has been estimated that more than 70% of long-term-care residents in Finland have severe or very severe cognitive decline (Finne-Soveri et al. 2015). Similarly, in the UK, up to 73% of NH residents have dementia (Alzheimer's Society, 2014).

In a Finnish register-based study, people with dementia used long-term care nine times more often (OR 9.30) than people without dementia (Forma et al. 2011).

2.2.6 PROGNOSIS OF DEMENTIA

Cognitive decline, disability and NPSs in dementia increase over time, although the rate at which the disease progresses varies (Strand et al. 2018). As the clinical course of dementia is gradual, it is useful to distinguish between various levels of severity. Dementia is most commonly divided into four stages: very mild, mild, moderate and severe dementia, in, for example, the clinical dementia rating (CDR) scale (Hughes et al. 1982). The CDR scale has been shown to correlate well with ADL and IADL scales, and moderately well with DSM-III-R criteria (Juva et al. 1994).

Survival after dementia diagnosis varies considerably and depends on various factors and their complex interaction (Brodaty et al. 2012). Worse cognition, male gender, higher number of types of medication, institutionalization, and age have been associated with increased death risk after dementia diagnosis (Garcia-Ptacek et al. 2014). Rates of survival and years of life lost vary between the different etiologies. People with VAD, DLB or PDD have the shortest survival times, followed by mixed dementia, and AD (Strand et al. 2018). A UK

population study revealed a median survival time from diagnosis of dementia to death of 4·1 years (Xie et al. 2008). In this study 72% of the participants had an MMSE score of less than 21/30 at the time of diagnosis. A more recent study carried out in Spain showed the median survival time from diagnosis of dementia to death to be 5·2 years (Garre-Olmo et al. 2019). These results are in line with those of a systematic review published in 2013, which reported median survival times from diagnosis to death ranging from 3.2–6.6 years (Todd et al. 2013). In a study carried out in Norway, VAD/DLB/PDD were associated with a life expectancy of 4.6 years in women and 4.7 years in men, whereas in cases of AD life expectancy was 7.5 years in women and 5.8 years in men (Strand et al. 2018).

2.3 FALLS

A fall is defined as an unexpected event whereby a person involuntarily comes to lie on the ground or another lower level with or without loss of consciousness (Lamb et al. 2005). The relationship between falls and dementia is complex. Both falls and cognitive impairment are prevalent among older adults, and the incidence of both increases with age (Bridenbaugh et al. 2015). Mobility problems and cognitive impairment often exist side by side and their temporal relationship appears to be bi-directional (Davis et al. 2015.)

Gait in older adults is a motor-cognitive task, where attention, executive functioning and memory are needed (Pichierri et al. 2011, Fernando et al. 2017). It has been argued that understanding the relationship between cognitive changes and gait disturbances could help to identify older adults at higher risk of progression to dementia, mobility decline or falls (Montero-Odasso et al. 2012, Modarresi et al. 2018).

2.3.1 EPIDEMIOLOGY OF FALLS

At least one-third of community-dwelling people over 65 years of age fall each year (Tinetti et al. 1988). People with dementia have a significantly higher risk of falling than those without dementia. The risk is twice as high in community-dwelling people with dementia as in those without dementia (Welmerink et al. 2010). The fall risk is even higher in nursing-home residents with dementia. Approximately half of nursing-home residents fall annually, a proportion that is two to three times that of community-dwelling residents (van Doorn et al. 2003).

The matter is of great importance, as the number of people with dementia is growing. Falls are major contributors to premature nursing-home placement (Tinetti et al. 1997). Higher dementia prevalence can lead to a higher prevalence of falls, which intrinsically leads to a higher number of fractures and head injuries, increasing healthcare and economic burdens, as well as individual suffering (Davis et al. 2015).

2.3.2 RISK FACTORS OF FALLS

Most falls are not the result of a single cause, but occur because of interaction of several risk factors (Berry et al. 2008). Risk factors of falls can be divided into intrinsic and extrinsic risk factors. Major identified intrinsic causes of a higher fall risk include previous falls, age, impaired cognition, impaired vision, and hearing and executive function deficits (AGS 2001). Musculoskeletal deficits and postural instability lead to impairments of gait and balance. In addition, psychotropic drug use as well as polypharmacy, alcohol use, malnutrition, neurocardiovascular diseases such as orthostatic hypotension, plus incontinence and arthrosis have been associated with falls (Hartikainen et al. 2007, Shaw et al. 2007, Herman et al. 2010, Deandrea et al. 2010, Tinetti et al. 2010, Ambrose et al. 2013). Extrinsic risk factors include, for example, lighting, furniture arrangements, clothing and footwear (AGS 2001).

Several drug classes have been shown to expose older people to the risk of falls, but the use of psychotropic medication is especially associated with falls among older people (Hartikainen et al. 2007, Woolcott et al. 2009, Olazarán et al. 2013, Seppälä et al. 2018, Yoshikawa et al. 2020) (Table 3. Studies on CNS medication and fall risk). The results of very large and intermediate-quality prospective cohort studies and case-control studies (n=8127–321 995) suggest a significantly increased risk of falls among the elderly (Seppälä et al. 2018). In a recent review the OR for falls in connection with various psychotropics were: 1.54 (95% CI 1.28–1.85) for all antipsychotics, 1.57 (95% CI 1.43–1.74) for all anti-depressants, 1.41 (95% CI 1.07–1.86) for TCAs, 2.02 (95% CI 1.85–2.20) for SSRIs, 1.42 (95% CI 1.22–1.65) for all benzodiazepines, 1.81 (95% CI 1.05–3.16) for long-acting benzodiazepines and 1.27 (95% CI 1.04–1.56) for short-acting benzodiazepines (Seppälä et al. 2018). Benzodiazepines have been considered to represent one of the main risk factors of falls and fractures in older people, but it seems that antidepressants and antipsychotics are no safer. These findings can partially be affected by preferential prescribing, such as prescribing SSRIs to frail older adults with a higher fall risk. There are very few data on other antidepressants. Low-dose trazodone seems to be no safer than benzodiazepines (Bronskill et al. 2018). Antipsychotic drugs as a group are also associated with an increased risk of falling. It has been reported that the relative risk of falls ranges between 1.21 and 11.4 (Hartikainen et al. 2007). Opioids seem to have major effect sizes as regards the risk of falls, fall-related injuries and fractures (Yoshikawa et al. 2020). According to the results of a recent trial among AD patients, the risk of falls among those on psychotropics may be reduced by long-term exercise (Perttilä et al. 2018).

Table 3. Studies on CNS medication and fall risk

Psychotropic class	Systematic review / meta-analysis	No. of studies, study types	Fall risk OR, 95% CI	Other findings, comments
Antipsychotics				
Antipsychotics as a group	Seppälä et al. 2018	75 O-studies Only 16 studies included in meta-analysis	1.54 (1.28-1.85)	52 studies were rated intermediate or high quality in the Newcastle Ottawa Scale. In these studies, 18 showed a positive association with falls. 6 studies in long-term care: OR 1.18 (0.97-1.43) Only one study provided data on injurious falls: OR 1.66 (0.17-16.21)
Atypical antipsychotics	Seppälä et al. 2018	5 studies	N.A.	All studies showed increased risk
Atypical antipsychotics	Seppälä et al. 2018	RCT=3 studies	N.A.	Risperidone in nursing home: 27% of users fall, 25% of nonusers fall Risperidone in residential care: HR for falls was dose-dependent: 2 mg/day HR 1.33 (0.83-2.15) Quetiapine in long-term care: 26% of users fall, 26% of nonusers fall
Antidepressants				
All antidepressants	Hartikainen et al. 2007	17 O-studies	N.A.	In five studies no elevated risk, in 12 studies increased risk. No significant differences between SSRIs and TCAs Risk was dose-dependent Even long-term use increases fall risk
All antidepressants	Seppälä et al. 2018	107 O-studies Only 22 studies included in meta-analysis	1.57 (1.43-1.74)	67 studies were rated intermediate or high quality in the Newcastle Ottawa Scale. In these studies, 48 showed a positive association with falls. No specific groups of antidepressants are safer in terms of fall risk 11 studies in long-term care: OR 1.46 (1.26-1.69) Only 5 studies provided data on injurious falls: OR 1.72 (1.51-1.96)
SSRIs	Seppälä et al. 2018	23 O-studies Only 4 studies included in meta-analysis	2.02 (1.85-2.20)	14 studies were rated intermediate or high quality in the Newcastle Ottawa Scale. In these studies, 12 showed a positive association with falls.
Tricyclics	Seppälä et al. 2018	24 O-studies Only 5 included in meta-analysis	1.41 (1.07-1.86)	16 were rated intermediate or high quality in the Newcastle Ottawa Scale. Of these, 8 showed a positive association with falls.

Table 3. Continued…

Psychotropic class	Systematic review / meta-analysis	No. of studies, study types	Fall risk OR, 95% CI	Other findings, comments
Anxiolytics				
Benzodiazepines	Woolcott et al. 2009	12 O-studies	1.57 (1.43-1.72)	Large systematic review including various psychotropics, antihypertensives and analgesics.
Benzodiazepines	Seppälä et al. 2018	67 O-studies Only 14 in meta-analysis 17 long-acting BZD studies 13 short-acting BZD studies	1.42 (1.22-1.65)	44 were rated intermediate or high quality in the Newcastle Ottawa Scale. Of these, 21 showed a positive association with falls. 3 studies in long-term care: OR 1.11 (0.84-1.47) Only one study provided data on injurious falls: OR 1.70 (1.03-2.81) Long-acting benzodiazepines might be more fall-risk-increasing 4 studies: OR 1.81 (1.05-3.16) In 4 studies on short acting BZDs: OR 1.27 (1.04-1.56)
Hypnotics/sedatives				
Hypnotics/sedatives	Seppälä et al. 2018	18 O-studies	N.A.	In 6 studies ATC codes were provided. Two of them showed positive association
Opioids				
All opioids	Yoshikawa et al. 2020	34 O-studies	N.A.	Opioids increase the risk of falls, injuries and fractures. Effect size in meta-analysis is large: 0.76 (95% CI 0.45-1.08)
Antiepileptics				
	Seppälä et al. 2018	30 O-studies 7 studies included in meta-analysis	1.55 (1.25-1.92)	Seizure-related falls were not excluded One study in long-term care: OR 0.69 (0.23-2.08) Only 2 studies reported injurious falls: OR 1.43 (1.10-1.86)
Gabapentinoids				
Pregabalin	Mukai et al. 2019 O-study	FAERS and JADER databases used for AE reporting	N.A.	>65y (n=1 962 359) ROR 2.32 (2.08-2.58) in FAERS >65y (n=244 361) ROR 7.77 (3.88-18.47)

O=observational study; FAERS= Food and Drug Administration Adverse Event Reporting System; JADER= Japanese Adverse Drug Event Report, BZD=benzodiazepine, ROR= reporting odds ratio

Polypharmacy, the use of five or more drugs, multiplies the risk of falling (Seppälä et al. 2018). In particular, concomitant use of several CNS-affecting drugs should be avoided. To my knowledge, there is only one study on gabapentinoids. Mukai et al. (2019) retrieved data from spontaneous reporting systems for adverse drug events in the US and Japan, and suggested that pregabalin significantly increases the risk of falls. There are controversial findings concerning the risk of falls in connection with antidementia drugs. In RCTs, no significant differences have been found between users and nonusers of ChEIs and memantine (Seppälä et al. 2018).

The use of psychotropic drugs, behavioral symptoms, impaired mobility and orthostatic hypotension have been shown to increase fall risk in nursing-home residents (van Doorn et al. 2003, Allan et al. 2009, Whitney et al. 2012, Kosse et al. 2015, Morley 2016, Cameron et al. 2018). Despite the high prevalence of both falls and NPSs among older adults with dementia there are relatively few studies exploring the association between NPSs and falls. The results of some studies have suggested that NPSs predict falls (Hasegawa et al. 2010, Suzuki et al. 2012, Sylliaas et al. 2012, Galik et al. 2018, Sato et al. 2018), but the evidence is scarce. Additionally, what is not yet clear is the impact of NPS severity on fall rate.

2.3.3 OUTCOMES OF FALLS

Most falls do not result in serious injury (van Doorn et al. 2003 Kosse et al. 2015, Galik et al. 2018). Only approximately 10% of those who fall suffer serious injuries such as fractures or head trauma (Galik et al. 2018). Minor injuries are more common and maybe present in 22–60% of fallers (Milat et al. 2011). Fall-related negative consequences are more likely among those with cognitive impairment (Thapa et al. 1996, Weller et al. 2004). Falls lead to higher rates of morbidity and mortality and are major contributors to immobility and premature nursing-home placement (Rubenstein 2006). Long-term-care residents have been reported to have the highest incidence

rates of hip fracture (Sugarman et al. 2002). The mean incidence rate of hip fractures across US long-term-care facilities in 2018 was 3.13 per 100 person-years (Zullo et al. 2018).

Interestingly, ChEI use has recently been associated with reduced fracture risk (Ogunwale et al. 2019, Tamimi et al. 2018). The suggested mechanism is that ChEIs may confer protection against fractures by accelerating bone healing and reducing both fracture complications and all-cause mortality post-hip fracture. These results are preliminary and all possible confounders were not adjusted for (e.g. dementia type, severity and frailty).

Even though not all falls lead to injury, every fall is significant, as a previous fall is an important risk factor of another fall (Rubenstein et al. 2006, Tinetti et al. 2010).

2.3.4 EXERCISE INTERVENTIONS TO PREVENT FALLS IN DEMENTIA PATIENTS

According to a recent Cochrane review there is high-certainty evidence that exercise programs reduce the rate of falls and the number of people experiencing falls when considering older people living in the community (Sherrington et al. 2019). The evidence for fall reduction in older people with dementia is not as consistent.

FINALEX, a Finnish Alzheimer disease exercise trial, an RCT carried out in Finland, showed that an intensive and long-term exercise program has beneficial effects on the physical functioning of patients with AD without increasing the total costs of health and social services or causing any significant adverse effects (Pitkälä et al. 2013). The participants were 210 home-dwelling patients with AD living with their spousal caregivers. In the trial more falls occurred among control participants, although no differences were recorded in the numbers of fractures or hospitalizations. This was one of the first studies that showed that exercise may reduce the incidence of falls in

patients with AD. A secondary analysis of FINALEX data revealed that exercise intervention had a significant effect on the risk of falling among participants with moderate or severe AD (CDR 2–3). Among participants in the intervention group, the rate of falls was 1.78 falls/person per year, while among those in the control group it was 3.76 falls/person per year (Öhman et al. 2016).

The effect of exercise interventions for preventing falls in older people in care facilities and hospitals is still uncertain. A recent study carried out in Sweden showed that a high-intensity functional exercise program, as a single intervention, did not prevent falls in people with dementia living in nursing homes (Toots et al. 2019). The authors proposed that in high-risk populations where multimorbidity and polypharmacy are common, a multifactorial fall-prevention approach may be required (Toots et al. 2019). Another reason for the contradictory results from this study could be the short duration of the intervention, just four months, compared with 12 months in the FINALEX intervention. A Cochrane review published in 2018 showed that exercise had little or no effect on the risk of falling in care facilities (Cameron et al. 2018). One problem with the review is that the quality of evidence in connection with individual interventions was generally rated as low or very low.

The results of a systematic review and meta-analysis concerning the effectiveness of exercise interventions in reducing falls in people with dementia suggested that physical exercise has a positive effect on preventing falls in older adults with cognitive impairment (Chan et al. 2015). Four of the seven studies involved showed a significant effect in reducing the fall rate. According to the authors, the core elements of successful intervention were multicomponent exercise (a combination of strength, endurance, and balance training), supervision of the training by a professional trainer, and an individually tailored exercise program adapted to the cognitive level of the participant (Chan et al. 2015). Probably because of attainment of sufficient muscle strength, progressive resistance training seemed to be the most effective exercise modality for improving gait speed (Van Abbema et al. 2015).

Tai Chi practice may also be effective for preventing falls in older adults (Huang et al. 2017). It may reduce the rate of falls by 43% and that of injury-related falls by 50% over 12 months (Lomas-Vega et al. 2017).

Current research evidence therefore suggests that increased physical exercise may not only decrease the number of falls but also slow the progression of cognitive decline and physical function (Teri et al. 2008, Pitkälä et al. 2013, Chan et al. 2015). Less is known about the effects of exercise on NPSs and if exercise can modify the risk of falls among people with dementia and NPSs.

2.4 HEALTH-RELATED QUALITY OF LIFE (HRQoL)

2.4.1 DEFINITION OF HRQoL

Understanding about quality of life (QoL) and HRQoL has advanced significantly over the past 25 years. Formerly, QoL in medicine typically concerned only objective measures, but in the early 1990s, a new understanding also included subjective well-being (Cummins et al. 2015). Nowadays WHO defines quality of life as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment (WHOQOL Group, 1994).

Health-related quality of life is also a multi-dimensional concept. It is considered a part of general QoL. There are four fundamental dimensions that are essential to any HRQoL measure. These include physical, mental/psychological, and social health, as well as global perceptions of function and well-being. Additional HRQoL domains considered important but not always necessary include pain, energy/vitality, sleep, appetite, and symptoms relevant to an intervention and the natural history of a disease or condition (Berzon et al. 1993). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQoL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Each approach has its strengths and weaknesses and may be suitable for different circumstances (Guyatt et al. 1993).

2.4.2 MEASURES OF HRQoL

Several measures for assessing HRQoL have been developed that reflect different conceptualizations of QoL (Ettema et al. 2005, Bowling et al. 2015). The use of different measures makes it difficult to compare study results (Table 4. Comparison of different measures of HRQoL). Another question concerns the use of self-reports or proxy measurements. It is known from previous research that there are differences between caregiver assessed and self-rated quality of life (Hoe et al. 2007, Hurt el at. 2008, Beerens et al. 2013, Hongisto et al. 2018). Patients tend to consider their quality of life to be higher than do caregivers. Both measures can be useful, as both can provide psychometrically sound data, but when patients who have difficulty in understanding the questions, for example as a result of severe dementia, are included, the application of proxy measures should be preferred. Examples of different measures of HRQoL in dementia, which can also be proxy-rated, include 15D (15-dimensional instrument for measuring HRQoL), SF-36 (short-form health survey with 36 questions), WHOQOL-Bref (World Health Organization Quality of Life instrument with 26 items) and QUALID (Quality of Life in Late-Stage Dementia Scale) measures (Sintonen 2001, Ware et al. 1992, WHOQOL Group 1998, Weiner et al. 2000).

Table 4. Comparison of selected measures of HRQoL

Dimension	15D	SF-36	WHOQOL-Bref	QUALID
Health and physical well-being	Mobility Vision Hearing, Breathing Sleeping Eating Excretion Discomfort and symptoms Vitality	Bodily pain General health Vitality	General health Pain and discomfort Dependency on medical substances and medical aids Mobility Sleep and rest Energy and fatigue	Has a facial expression of discomfort Appears physically uncomfortable Enjoys eating
Psychological well-being	Depression, Distress Mental function	Mental health perceptions	Positive feelings Negative feelings Self-esteem Bodily image and appearance Spirituality, religion and personal belief Thinking, learning, memory and concentration	Smiles Appears sad Cries Appears emotionally calm and comfortable Is irritable or aggressive Makes statements or sounds that suggest discontent, unhappiness or discomfort
Social relationships	Speech (communication) Sexual activity	Social functioning	Personal relationships Sexual activity Social support	Enjoys touching/being touched Enjoys interacting or being with others
Productivity and functioning	Usual activities	Physical functioning Role limitations because of health problems	Activities of daily living Work capacity Participation in and opportunities for recreation and leisure activities	
Environment and material well-being			Freedom, physical safety and security Physical environment Financial resources Home environment Opportunities for acquiring new skills and information Transport Health and social care: accessibility and quality	

15D (Sintonen 2001), SF-36 (Ware and Sherbourne 1992), WHOQOL-Bref (WHOQOL Group 1998), QUALID (Weiner et al. 2000) used for persons with dementia.

2.4.3 HRQoL IN DEMENTIA

Without a cure, the main question in dementia care is how to promote well-being and maintain an optimal QoL (Whitehouse et al. 2003). Unmet needs of people with dementia living in nursing homes have been linked to worsening NPSs and reduced QoL (Cohen-Mansfield et al. 2015). In a literature review, self-reported needs and experiences of people with dementia in nursing homes were explored, revealing eight specific themes to be linked to QoL (Shiells et al. 2019). These themes were activities, maintaining previous roles, reminiscence, freedom and choice, appropriate environment, meaningful relationships, support for grief and end-of-life care.

2.5 SUMMARY OF THE LITERATURE

Neuropsychiatric symptoms are among the most complex, stressful, and costly aspects of dementia care. They have been shown to lead to higher morbidity and mortality rates, hospital stays, and early placement in long-term care (Wancata et al 2003, Kales et al. 2005, Mar et al. 2019).

The use of psychotropic drugs is common in people with dementia, especially those in long-term care. They are mainly used to manage NPSs, although their efficacy and balance of harms and benefits remains uncertain. The amount of evidence on the harms of psychotropic drugs, including falls, has increased in recent years. We lack information on whether or not this has changed prescribing among older adults with dementia in long-term care. Longitudinal studies can offer important information on how the use of these types of medication has changed over time. Systematic assessment of adverse effects is also essential in order to improve the care of older adults with dementia.

Factors behind falls have been extensively studied, and it is well known that people with dementia have a higher risk of falling (Tinetti et al. 1988, Fernando et al. 2017). Individual risk factors of falls are multiple and vary between community- and institution-dwelling older adults with cognitive impairment (Allan et al. 2009, Kröpelin et al. 2012, Fernando et al. 2017). There is evidence that the use of psychotropic drugs increases fall risk. The results of some studies have also suggested that NPSs predict falls (Hasegawa et al. 2010, Suzuki et al 2012, Sylliaas et al. 2012). What has not been established yet is the interplay of NPSs and psychotropics and the relationship between NPSs and falls.

Neuropsychiatric symptoms are known to affect the quality of life of both the patient and the caregiver. What remains unclear are the factors that explain this association and whether or not these factors are different in frail older adults in later stages of dementia.

In summary, the relationships between NPSs and falls, psychotropic drug use and quality of life in dementia are complex. There is continuous interplay between the different factors (Figure 4). Gaps in the current literature justify a more detailed study looking at the factors modifying these relationships.

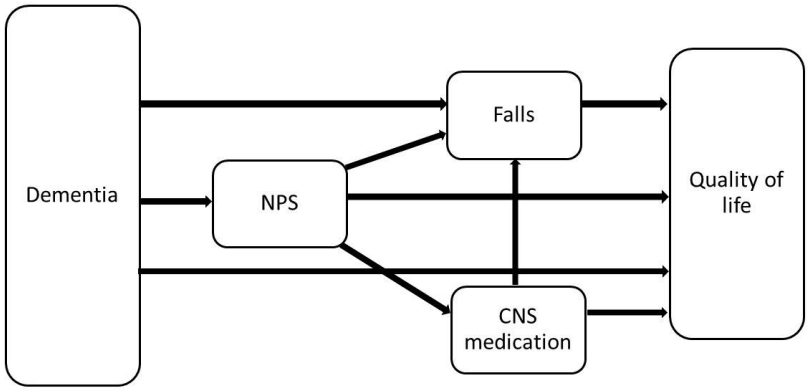


Figure 4. Interplay between neuropsychiatric symptoms, medication, falls, and quality of life among older adults with dementia

3 AIMS OF THE STUDY

The aim of this study was to examine the relationships between NPSs, falls, psychotropic drug use, and HRQoL among people with dementia. Specific research questions in the individual studies were as follows:

1. What is the relationship between NPSs and falls in older people with cognitive impairment? (Studies I and IV)

2. Does long-term exercise intervention modify the risk of falling associated with NPSs in community-dwelling people with AD? (Study I)

3. Do psychotropic drugs modify the relationship between NPSs and falls among older people with cognitive impairment in long-term care?

4. What are the trends in prevalence of use of psychotropic medication and opioids according to residents' dementia status in institutionalized older adults in Helsinki over a 14-year period? (Study II)

5. What is the association between NPSs and HRQoL, and, further, does the severity of dementia modify this relationship? (Study III)

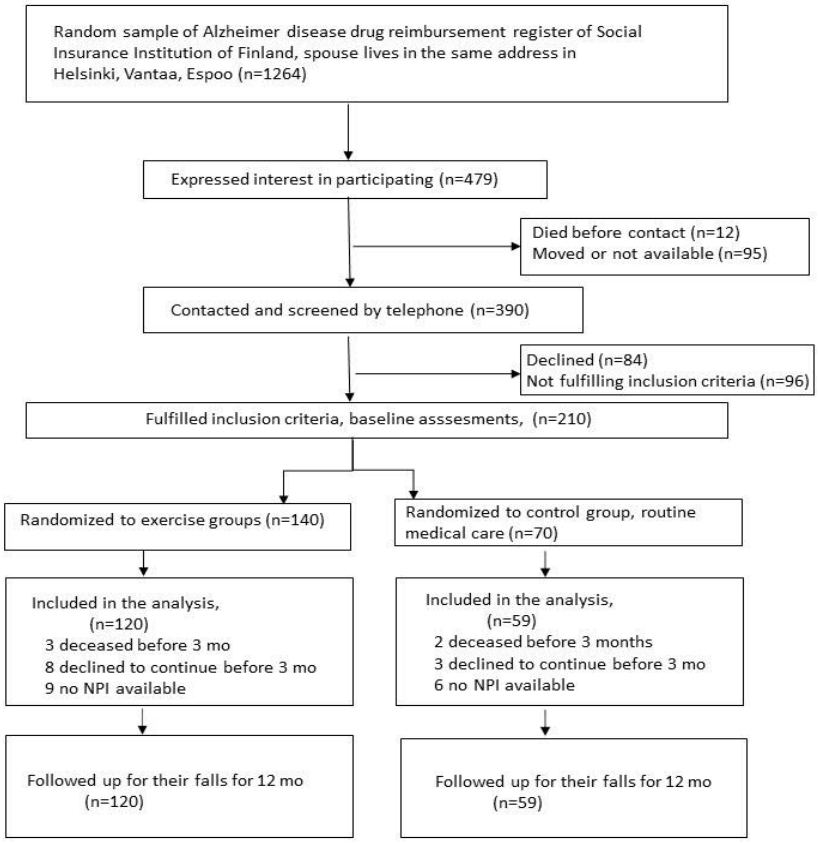
4 METHODS

4.1 PARTICIPANTS

4.1.1 STUDY I

The drug reimbursement register of the Social Insurance Institution of Finland was used to recruit community-dwelling people with AD living in the cities of Helsinki, Vantaa, and Espoo to an exercise trial in 2008. For an individual to be included in this register, a neurologist or a geriatrician has diagnosed him or her with AD based on NINCDS-ARDRA criteria (McKhann et al. 2011). A letter offering the possibility of participating in the trial was mailed to all 1,264 of these individuals. Those who expressed an interest in participating (n = 497) received a postal questionnaire asking for information on inclusion criteria: established AD, aged 65 and older, living with a spouse at home, no diagnosed terminal disease, and walking independently with or without a mobility aid. Participants were also required to have at least one of the following signs of frailty: one or more falls in the past year, a decrease in walking speed, and unintentional weight loss. After receiving the completed questionnaire, the study nurse conducted a telephone interview with the spousal caregiver to ensure that all inclusion criteria were met. Two hundred ten participants met the inclusion criteria and were enrolled in the study (Figure 5). In a sub-study, we included all participants (n = 179) with at least three months of follow-up and whose spousal caregiver had completed the Neuropsychiatric Inventory (NPI).

Figure 5. Flow chart of Study I.



4.1.2 STUDY II

In this study data from four cross-sectional studies exploring medication use and nutrition in institutional settings in Helsinki were combined. The studies were conducted among all NH residents of Helsinki in 2003 (n=1987), 2011 (n=1576), and 2017 (n=791), and among all assisted-living facility (ALF) residents of Helsinki in 2007 (n=1377), 2011 (n=1586), and 2017 (n=1752). The 2003, 2011, and 2017 samples comprised 94%, 81%, and 68% of the total NH population, and the 2007, 2011, and 2017 samples 66%, 64%, and 64% of the total ALF population, respectively. The nonparticipants were those having moderate-severe dementia (CDR 2-3) with no close proxy to give informed consent, those who refused to take part, and those who did not provide a complete medication list (Figure 6).

In Finland, ALFs provide round-the-clock care, with a registered nurse in charge. This is similar to the care provided in NHs, but ALFs are designed to resemble residents' own home environment to a greater extent. ALFs include both apartments and group homes for people with dementia. However, the number of registered nurses is lower in ALFs than in traditional NHs. As a result of organizational change of long-term care in Helsinki the number of NH beds in Helsinki significantly declined from 2003 to 2017, and this has been compensated for by an increase in the number of ALF beds. The national recommendation for minimum staffing levels in 24-hour care is 0.6 employees per resident in NHs and 0.5 in ALFs.

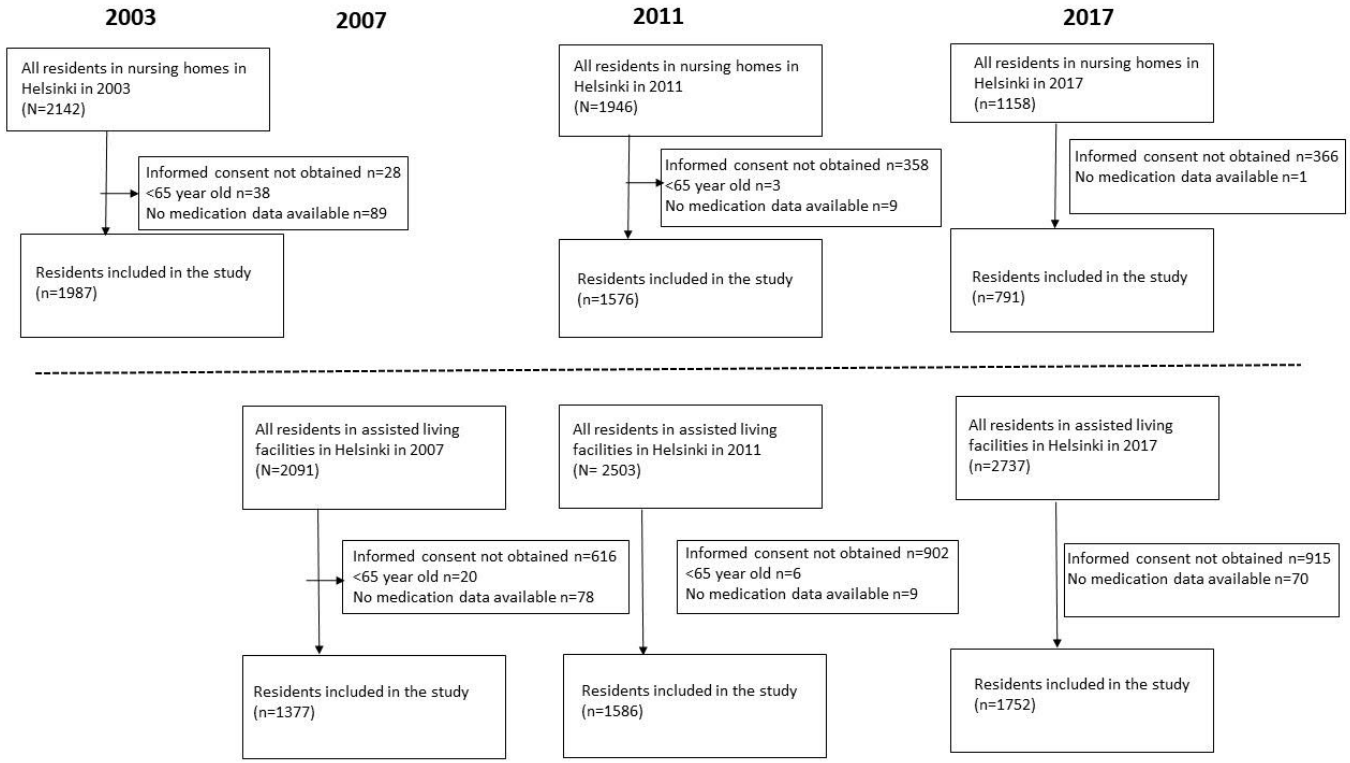
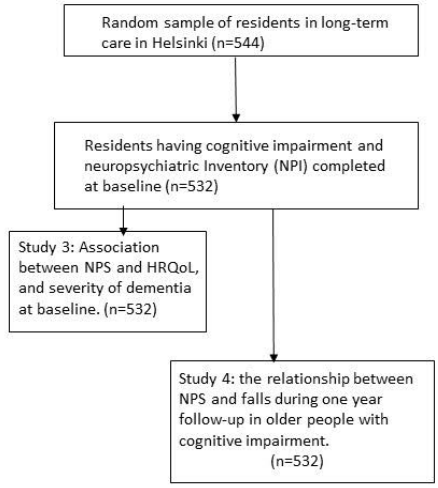


Figure 6. Flow chart of Study II. Above the dashed line, nursing homes and below the line, assisted-living facilities. Colums show the year of assessment.

4.1.3 STUDIES III AND IV

The participants were recruited to these studies from institutional settings in Helsinki in 2017. The study was offered to all 54 long-term-care facilities in Helsinki including both NHs and ALFs. Of these, the first 18 to volunteer were included. We recruited and assessed consecutive participants from each of these facilities until we reached a targeted sample of 544. The participants' baseline assessment occurred between February 2018 and August 2018. All participants who completed the Neuropsychiatric Inventory (NPI) at baseline (n=532) were included in both studies. For Study IV the participants were followed for 12 months or until death as regards falls whichever came first (Figure 7).

Figure 7. Flow chart of Studies III and IV



4.2 STUDY I INTERVENTION

Before intervention, a geriatrician assessed each participant's health status to ensure their safety. The intervention groups exercised under the supervision of a physiotherapist for one hour twice a week over one year in their own homes or at the gym. The exercise sessions comprised strength, balance, endurance, and multitask training, including training on a restorator cycle, Nordic walking, stair climbing, picking up items from the floor, and talking while walking. The control group received normal community care (rehabilitation in the public healthcare system, including physiotherapy if needed).

4.3 DATA COLLECTION

In Study I, which concerned the relationship between NPSs and falls in home-dwelling older adults with AD, a registered nurse and a physiotherapist assessed the participants and their spousal caregivers four times (baseline, and at three, six and 12 months). The assessors were blinded to group allocation.

In Study II, which concerned temporal trends in the prevalence of use of psychotropics and opioids, and sedative load in long-term-care settings over a 14-year period in relation to the residents' dementia status, nurses in each long-term-care setting were trained thoroughly to collect data and perform the assessments.

In Studies III and IV, which concerned the association between NPSs and HRQoL and the relationship between NPSs and falls, respectively, trained study nurses collected data and performed the assessments. The author participated and supported the nurses in their assessments and data collection.

In all studies data on demographic factors (age, sex, and education), diagnoses, and medication use were collected from medical records on the assessment day. Only regularly used types of medication were considered. Medication use was considered regular if there was a documented regular sequence of administration. The Charlson Comorbidity Index was used to calculate each resident's burden of comorbidity (Charlson et al. 1987).

4.4 MEASURES

4.4.1 NEUROPSYCHIATRIC MEASURES

To evaluate NPSs the Neuropsychiatric Inventory (NPI) (Cummings 1997) tool was used in Studies I, III and IV. The original NPI includes 10 common dementia NPSs (aberrant motor behavior, agitation, anxiety, apathy, disinhibition, delusions, dysphoria, euphoria, hallucinations, irritability). For each symptom, the severity is multiplied by the frequency, and the sum score provides the total NPI score (range 0 to 120). According to previous studies, an NPI score >3 is considered to indicate the presence of clinically significant symptoms (Schneider et al. 2001, Steinberg et al. 2004, Aalten et al. 2008). In Studies III and IV the participants were divided into groups according to their NPI points: no significant NPSs (NPI 0–3), low NPS burden (NPI 4–12), and high NPS burden (NPI>12). Specific scores for four different subsyndromes, i.e. "psychosis" (delusion, hallucinations), "hyperactivity" (agitation, euphoria, disinhibition, irritability, aberrant motor behavior), "affective symptoms" (depression and anxiety), and "apathy" (apathy) were also calculated separately, as described by Aalten et al. (Aalten et al. 2008).

The Cornell depression scale was used to assess depressive symptoms (Alexopoulos et al. 1988). The scale consists of 19 items including questions about mood-related signs, behavioral disturbances, physical signs, cyclic functions, and ideational disturbances. Evaluation is based on interviews of both patient and/or nursing staff member. All items are evaluated as either

0=absent, 1=mild or intermittent, or 2=severe. The total score ranges from 0 to 38, in which lower scores refer to no depression or mild depressive symptoms and scores of 13 and higher refer to more severe depression (Alexopoulos et al. 1988).

4.4.2 COGNITIVE MEASURES

Global cognition was measured by using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) and the Clinical Dementia Rating (CDR) scale (Hughes et al. 1982). Each instrument has its advantages and disadvantages. It has been suggested that the CDR score reflects actual functioning better than the MMSE score (Juva et al. 1995).

The MMSE is an instrument widely used in clinical practice as well as in research (Tombaugh et al. 1992) to assess the severity of cognitive impairment and to document cognitive changes that occur over time. The MMSE was designed to examine cognitive functions, including orientation, attention, recall, language, ability to follow instructions, ability to produce a meaningful written sentence, and visual construction. The maximum MMSE score is 30 points. Age, education, and cultural background affect the test results and need to be taken into consideration when interpreting the results (Tombaugh et al. 1992, Ylikoski et al. 1992, O'Bryant et al. 2008). In people with a neurocognitive disorder, MMSE points 0–11 usually refer to severe dementia, 12–17 to moderate dementia, 18–23 to mild dementia, and 24–30 to MCI or normal cognitive functioning (Memory Disorders: Current Care Guidelines, 2017).

The Clinical Dementia Rating (CDR) scale is a tool which has demonstrated high validity and reliability (Hughes et al. 1982). It is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to AD and related dementias. The domains include memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care. Each category is marked independently. Memory is considered

the primary category and all others are secondary. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant (e.g., family member or nurse). The CDR score ranges from 0–3 (0 = Normal, 0.5 = Very Mild Dementia, 1 = Mild Dementia, 2 = Moderate Dementia, 3 = Severe Dementia) (Morris 1993).

4.4.3 FUNCTIONAL MEASURES

In Study I, functional status was evaluated by using the Functional Independence Measure (FIM) (Pollak et al. 1996) and the Short Physical Performance Battery (SPPB) (Guralnik et al. 1994). The FIM consists of 18 categories of which five concern cognitive functioning and 13 concern physical functioning. Each category is rated on a scale from 1 to 7, in which 1 refers to total assistance required and 7 refers to full independence. The total score ranges from 18 to 126 points. The lower the score, the more likely the person needs assistance.

In Study II, function and mobility were assessed by using the Mini Nutritional Assessment (Guigoz et al. 2002) item on mobility and categorized as either 0= "unable to get out of a bed, a chair, or a wheelchair without the assistance of another person" or 1="able to get out of bed or a chair without help."

In Studies III and IV, function was evaluated by using the Barthel Index (BI) (Mahoney et al. 1965). The BI covers 10 personal activities: feeding, moving from wheelchair to bed and returning, personal toileting, getting on and off a toilet, bathing, walking on a level surface (or propelling a wheelchair if unable to walk), dressing and undressing, ascending and descending stairs, controlling the bladder and controlling the bowel. Each item is rated thus: 0=unable, 5=needs help, 10=independent. The maximum BI score is 100. BI scores of 0–20 indicate total dependency, 21–60 indicate severe dependency, 61–90 indicate moderate dependency, and 91–100 indicate slight dependency (Shah et al. 1989).

In Study III, frailty was also assessed. Phenotypic frailty status was defined by using modified Fried criteria (Perttilä et al. 2017), i.e. four criteria as follows: (1) shrinking was based on weight loss of ≥ 5% in the preceding year, (2) physical weakness was based on self-reported or care-staff evaluation of difficulty in carrying a bag of groceries, (3) exhaustion was based on self-reported or care-staff evaluation of low energy during the preceding four weeks, and (4) physical inactivity was based on the response to the question: "Do you/does the resident exercise regularly weekly?" A negative response meant physical inactivity. The sum of fulfilled criteria classified the person as "not frail" (no criteria),"pre-frail" (1–2 criteria), or "frail" (3–4 criteria).

4.4.4 NUTRIONAL MEASURES

In all studies Mini Nutritional Assessment (MNA) was used to assess and grade each participant's nutritional status (Guigoz et al. 2002). The MNA consists of 18 questions of which six are for screening and twelve are for assessment. For each question the lowest score is 0 and the highest score ranges from 1 to 3. Total points come to 0 to 30, of which points <17 indicate malnutrition, points from 17 to 23.5 indicate risk of malnutrition, and points from 24 to 30 indicate normal nutritional status.

4.4.5 HRQoL MEASURES

The 15D instrument was used in Study III to assess HRQoL. It is a generic 15-dimensional measure. It has been internationally validated in various population samples (Sintonen 2001). It correlates well with other HRQoL measures such as SF-36 (Ware et al. 1992) and EQ-5 (Hawthorne et al. 2001). 15D includes the following 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each dimension is divided into five levels. A single weighted index can be constructed from these 15 dimensions. The single index score of 0–1

represents overall HRQoL. The maximum score is 1 (no problems on any dimension) and the minimum score is 0. Usually the 15D paperwork is filled in by the subject being assessed, but it may also be filled in by the interviewer of the subject or his/her proxy. The 15D instrument shows good discriminant validity among various aged populations, and also prognostic validity (Strandberg et al. 2006).

4.4.6 MEDICATION

To assess medication use, the Anatomical Therapeutic Chemical (ATC) classification system was used in all four studies. It classifies drugs into different categories according to their therapeutic, pharmacological, and chemical properties, and the organ or system on which they act (WHO 2020). ATC central-nervous-system drugs (code N) include psychotropics (N05), which are divided further into antipsychotics (N05A), anxiolytics (N05B), and hypnotics and sedatives (N05C). Antidepressants are classified as group N06A. In all four studies assessment was made of the use of Alzheimer's medication (N06D), including cholinesterase inhibitors (N06DA) and/or memantine (N06DX01), because they are often used in connection with NPSs, as alternatives to psychotropics.

In Study II, pain medication use was also assessed. The drugs included in the study were opioids (N02 A), which were further categorized as weak opioids (codeine, buprenorphine, tramadol) and strong opioids (morphine, fentanyl, oxycodone), as well as paracetamol (N02BE01) and nonsteroidal anti-inflammatory drugs (NSAIDs) (M01 A). Pregabalin (N03AX16), gabapentin (N03AX12), carbamazepine (N03AF01), oxcarbazepine (N03AF02), and valproic acid (N03AG01) were also included in order to assess the overall use of sedative medication.

4.4.7 FALLS

In Study I, the participants' spouses recorded falls during the one year of follow-up in daily fall diaries. The number of falls was noted at each study visit. A fall diary has been found to be the most valid method to record the number of falls (Hannan et al. 2010)

In Study IV, records of all falls were retrieved from nurses' daily electronic charts over one year.

4.5 ETHICAL CONSIDERATIONS

The Ethics Committee of Helsinki University Central Hospital approved the study protocols for all studies. All participants, and in the case of Study I their spousal caregivers, provided written, informed consent. In cases of significant cognitive decline (CDR 2 or 3), the spouse (Study I) or the participant's closest proxy (in Studies II, III and IV) gave consent.

4.6 STATISTICAL METHODS

Data are presented as means with standard deviations (SDs) or as counts with percentages. In Study I, baseline data of the groups were compared by using the t-test, the bootstrapped-type t-test, Wilcoxon's rank-sum test, the Chi-square test, or the Fisher–Freeman–Halton test, as appropriate. In Studies II–IV statistical significance for the unadjusted hypothesis of linearity across characteristics of the study participants were evaluated by using the Cochran–Armitage test for trend, analysis of variance (ANOVA), or logistic (ordinal) models, with appropriate contrast. A bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of

violation of assumptions (e.g. non-normality) in Study IV. The normality of variables was evaluated by using the Shapiro–Wilk W test.

In Studies I and IV the numbers of falls and incidence rates were calculated assuming a Poisson distribution. Adjusted incidence rates and incidence rate ratios (IRRs) were calculated using a Poisson regression model. In Study I the model included gender, age, MMSE score, and SPPB totals as covariates. In Study IV the model included gender, age, and mobility as covariates. Poisson regression analysis was carried out using goodness-of-fit of the model, and the assumption of overdispersion in the Poisson model was tested using the Lagrange multiplier test. In Study IV the possible nonlinear relationship between all the falls and the NPI total score was assessed by using a 3-knot-restricted cubic (placed according to Harrell's recommended percentiles) spline Poisson regression model.

In Study II the number of types of medication was calculated using a Poisson regression model and the proportion of opioid users was evaluated by using a logistic model. The models included age, gender, Charlson comorbidity index, and mobility as covariates. The bootstrap method was used when the theoretical distribution of the test statistics was unknown, or in the case of violation of assumptions (e.g. non-normality).

In Study III the adjusted hypothesis of linearity (orthogonal polynomial) in the relationship between NPI and 15D scores according to CDR classes was evaluated using analysis of co-variance (ANCOVA) adjusted for age, sex, and the Charlson Comorbidity Index. In cases of violation of assumptions (e.g. non-normality), a bootstrap-type test was used (5000 replications). Adjusted (partial) correlation coefficients were calculated by Pearson's method with bootstrapped 95% confidence intervals.

All analyses were performed using Stata version 15.0 or 16.0 software (Stata Corp., College Station, TX).

5 RESULTS

5.1 CHARACTERISTICS OF SAMPLES

There were four large samples of older adults in this study (Table 5. Baseline characteristics of the participants). The sample sizes ranged from 179 to 4715.

Table 5. Baseline characteristics of the participants

Variable	**FINALEX RCT 2008-2010 n=179**	**Nursing homes 2003-2017 n=4354**	**Assisted living 2007-2017 n=4715**	**Long-term care 2018-2019 n=532**
Study	1	2	2	3, 4
Age, mean	78	84	84	84
Women, % (n)	38.5 (69)	78.6 (3422)	75.7 (3567)	79.7 (424)
CCI, mean	2.6	2.1	2.2	2.1
Not able to move independently, % (n)	0 (0.0)	46.9 (2042)	22.7 (1273)	57.5 (306)
MNA, % (n)				
>23.5 well nourished	27.4 (49)	27.1 (1180)	16.2 (764)	14.3 (76)
17-23.5 at risk	70.9 (127)	62.9 (2739)	63.5 (2994)	66.7 (355)
<17 malnourished	1.7 (3)	9.9 (431)	20.3 (957)	16.4 (87)
CDR, % (n)				
0.5–1	35.8 (64)	38.2 (1663)	55.4 (2612)	9.3 (49)
2	50.8 (91)	29.1 (1267)	23.4 (1103)	27.0 (144)
3	13.4 (24)	32.7 (1424)	21.2 (1000)	63.7 (339)
No. of regularly used medications, mean	6.9	7.8	8.6	8.5
Taking a psychotropic medication, % (n)	31.9 (57)	68.1 (2965)	65.6 (3093)	87.0 (463)
On cognitive enhancers, % (n)	97.5 (175)	22.6 (984)	39.3 (1853)	43.3 (230)

CCI=Charlson Comorbidity Index (Charlson et al. 1987); MNA=Mini Nutritional Assessment (Guigoz et al. 2002); CDR=Clinical Dementia Rating (Hughes et al. 1987). In nursing-home and assisted-living cohorts just the CDR memory item was used. Psychotropics included antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics and sedatives (N05C). Cognitive enhancers included cholinesterase inhibitors (N06DA) and/or memantine (N06DX01).

The mean ages ranged from 78 to 84 years. Females comprised the majority of participants in three of the four samples. Only in the FINALEX trial were males prominent (61.5%), due to the fact that the inclusion criteria included a spouse living at the same address.

The participants had a high number of comorbidities (CCI range 2.1 to 2.6), which in turn corresponds to a moderate risk of one-year mortality. All participants in the FINALEX trial were able to move independently, as this was one of the inclusion criteria. In the nursing-home sample in 2003–2017 about 47% were unable to move independently, and the respective figure in assisted-living facilities in 2007–2017 was 23%. In the most recent sample from all long-term units (in 2018–2019), almost 60% were unable to move without help.

A risk of malnutrition was common in all samples. A majority (72.6%) of home-dwelling AD patients were at risk of malnutrition or were malnourished. Respective figures were 72.8% in nursing homes, 83.8% assisted-living facilities and 83.1% in long-term-care wards.

The participants varied in the severity of cognitive impairment. Most of the participants in the FINALEX trial had mild to moderate dementia (CDR 0.5–2), whereas almost all long-term-care residents had moderate to severe dementia (CDR 2–3). The participants were also given a high number of drugs; mean range from 6.9 to 8.6. Of the participants, 32–87% were taking psychotropics, and 23–98% cognitive enhancers.

The baseline table shows important temporal changes in the long-term-care resident profile: both mobility disabilities and cognitive impairment are more prevalent and more severe in the most recent sample.

5.2 RELATIONSHIP BETWEEN NPSs AND FALLS IN OLDER PEOPLE WITH COGNITIVE IMPAIRMENT (STUDIES I AND IV)

In both Study I and Study IV falls had a clear relationship with NPSs, measured by the total NPI score. According to the results of Study IV, psychotropic drug use did not modify this association. In Study I the incidence of falls increased linearly with NPI score in the control group, whereas it stayed at the lower level irrespective of NPI score in the intervention group.

In Study IV the NPI total score showed a curvilinear association with the incidence rate of falls per person-year (Figure 8).

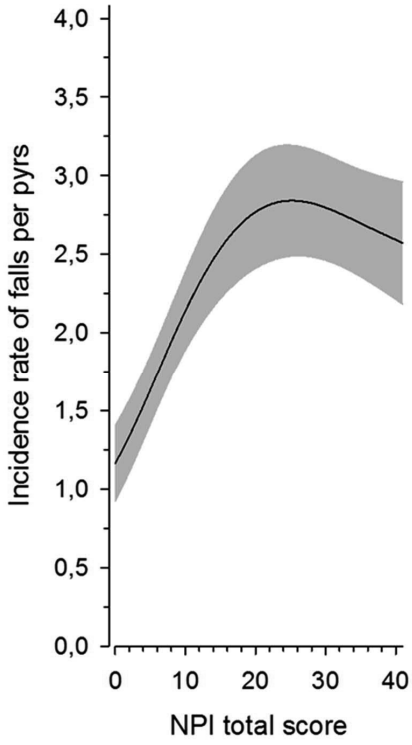


Figure 8. Incidence of falls per person-years (pyrs) according to the Neuropsychiatric Inventory (NPI) total score. Adjusted for age, sex and mobility.

When comparing the three NPS groups (NPI 0–3, NPI 4–12, NPI >12), they did not differ as regards their age, sex, or MMSE and CCI scores. However, higher NPI points were associated with better mobility and a higher number of types of psychotropic medication (Table 6).

In Study IV the total follow-up time was 446.8 person-years, with a mean time of 0.84 (range 0.01–1.00) years per person. Approximately a third of the participants died before the end of the follow-up year: 28.7% in the group with no significant NPSs, 33.2% in the low-NPS-burden group, and 33.7% in the high-NPS-burden group (p=0.56). However, all these participants' falls were recorded during their follow-up. Altogether, 606 falls occurred during the follow-up period: 330 in the high-NPS-burden group, 188 in the low-NPS-burden group, and 88 in the no-NPS group. Of the 606 falls, 121 led to injuries, 42 to injuries needing hospitalization and 20 to fractures.

Falls and injuries increased significantly with neuropsychiatric symptom burden. Using the no significant NPSs group as a referent, the low-NPS-burden group had an IRR per SD for falls of 1.64 (95% CI 1.27–2.12, adjusted for age, sex and mobility), whereas in the high-NPS-burden group the IRR per SD was 2.43 (95% CI 1.91–3.08, adjusted for age, sex and mobility) (p for linearity < 0.001).

Table 6. Characteristics of residents grouped by severity of neuropsychiatric symptoms according to Neuropsychiatric Inventory (NPI) total score

	NPI 0-3 N=167	NPI 4-12 N=181	NPI >12 N=184	P for trend
Age, mean (SD)	84 (8)	85 (7)	85 (7)	0.35
Women, n (%)	132 (79)	139 (77)	153 (83)	0.31
Charlson Comorbidity Index, mean (SD)	2.1 (1.3)	2.2 (1.3)	2.0 (1.3)	0.28
Barthel Index, mean (SD)	21 (24)	26 (23)	33 (25)	<0.001
Mobility				<0.001
Able to walk without help	44 (26)	73 (40)	109 (59)	
Able to walk only with help	55 (33)	53 (29)	52 (28)	
Bed-ridden	68 (41)	55 (30)	23 (13)	
CDR,n (%)				0.35
0.5-1	26 (16)	13 (7)	10 (5)	
2	37 (22)	51 (28)	57 (31)	
3	104 (62)	117 (65)	117 (64)	
MMSE, mean (SD)	6.8 (8.6)	6.4 (7.4)	6.9 (7.6)	0.89
Number of medications, mean (SD)	7.9 (3.6)	8.8 (3.5)	8.8 (3.8)	0.031
Number of Psychotropic medications, mean (SD)	1.8 (1.3)	2.1 (1.5)	2.3 (1.4)	<0.001
On Alzheimer medication, n (%)	62 (37)	82 (45)	87 (48)	0.041
No major vision deficits n, %	129(77)	146(81)	153(83)	0.16
No major hearing deficits n, %	155(93)	176(97)	181(98)	0.007
NPI total, mean (SD)	0.7 (1.1)	7.9 (2.8)	28.8(14.1)	
NPS subgroups, mean (SD)				
Psychosis	0.2 (0.6)	1.1 (1.9)	4.8 (6.1)	
Hyperactivity	0.3 (0.7)	4.7 (3.7)	15.6 (9.8)	
Affective	0.2 (0.6)	1.1 (1.9)	5.5 (5.7)	
Apathy	0.1 (0.4)	1.0 (2.3)	2.9 (4.0)	

Charlson Comorbidity Index (Charlson et al. 1987); Barthel Index (Mahoney et al. 1965); CDR=Clinical Dementia Rating (Hughes et al. 1987); MMSE= Mini Mental State Examination (Folstein et al. 1975); Psychotropics included antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B), hypnotics and sedatives (N05C); Alzheimer medication included cholinesterase inhibitors (N06DA) and/or memantine (N06DX01); NPI= Neuropsychiatric Inventory (Cummings et al. 1997); Neuropsychiatric symptoms subgroups (Aalten et al. 2007).

There were differences in the associations between neuropsychiatric subsyndromes and the IRRs of falls and fall-related negative consequences (Figure 9). Psychosis and hyperactivity subgroups were associated with a higher IRR of falls and injuries, whereas apathy showed a protective association against falls but not injuries. Affective symptoms did not predict falls nor injuries. Psychosis, hyperactivity and affective-symptom subgroups were associated with a higher IRR of hospitalization, whereas apathy was not. None of the subgroups predicted fractures.

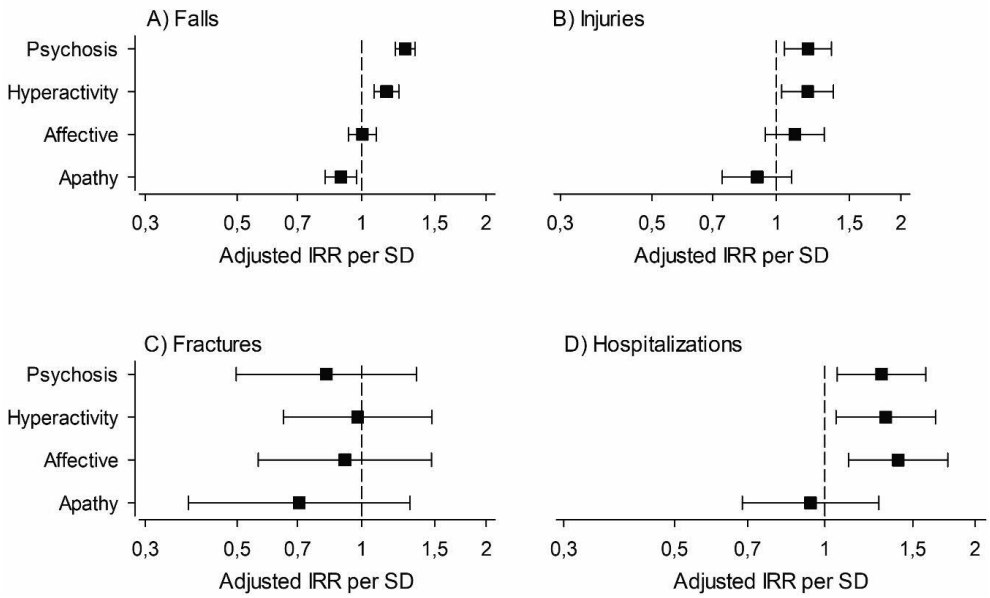


Figure 9. Association between neuropsychiatric symptoms subgroups and incidence rate ratio (IRR) of falls and fall related negative consequences per 1-SD. Adjusted for age, sex, and mobility.

5.3 INTERACTION EFFECT OF EXERCISE INTERVENTION ON THE RISK OF FALLING ASSOCIATED WITH NPSs IN COMMUNITY-DWELLING OLDER ADULTS WITH AD (STUDY I)

In the FINALEX study the intervention and control groups did not differ in their characteristics at baseline. Whereas the incidence of falls increased linearly with NPI score in the control group in Study I, the exercise-intervention group showed no such relationship. The fall rate was 1.48 (95% CI 1.26–1.73) per person-year in the intervention group compared with 2.87 in the control group (Figure 10). Adjusted for age, sex, MMSE score, and SPPB score, the IRR was 0.48 (95% CI 0.39–0.60, $p < 0.001$) for the intervention group compared with the control group. Fall rates were significant in connection with group ($p < 0.001$) and NPI total score ($p < 0.02$); the interaction effect was also significant ($p = 0.009$, adjusted for sex, age, MMSE score, SPPB score, and psychotropic medication use).

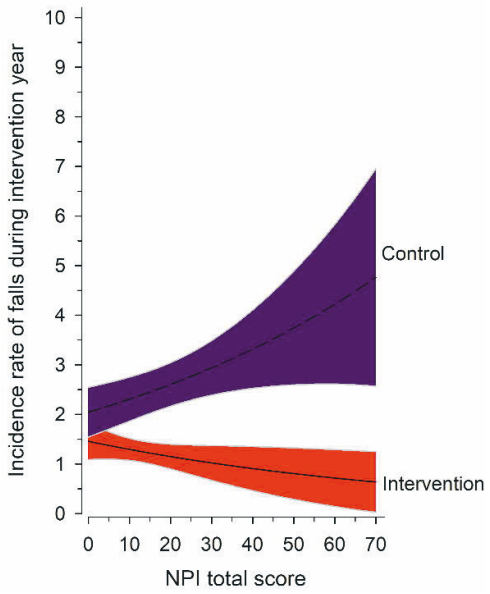


Figure 10. Incidence rate of falls in the exercise-intervention and control groups according to Neuropsychiatric Inventory (NPI) score.

5.4 TRENDS IN PREVALENCE OF PSYCHOTROPIC MEDICATION, OPIOIDS, AND OTHER SEDATIVES ACCORDING TO RESIDENTS' DEMENTIA STATUS (STUDY II)

Study II concerned 14-year trends in the prevalence of medication types commonly used for the treatment of NPSs in long-term care in Helsinki. Both in NHs and in ALFs the proportion of those with dementia and those unable to move independently increased over the years. In both settings the mean number of regularly used types of medication increased over the years (see Tables 1 and 2 in Article II). The prevalence of psychotropic medication use declined significantly in the NHs ($p < 0.001$), whereas in ALFs there was no linear trend ($p=0.15$). The prevalence of regular psychotropic medication use in NHs fell from 81.3% in 2003 to 60.9% in 2017. In ALFs, the prevalence remained more stable; 64.6% in 2007 and 63.6% in 2017.

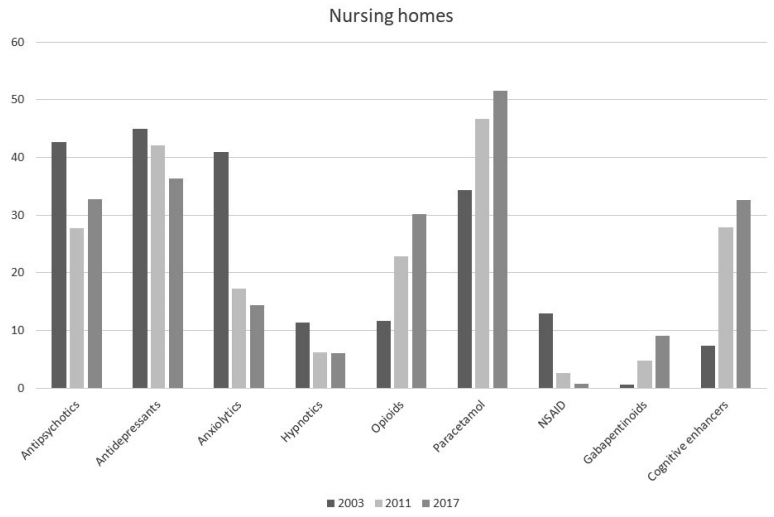


Figure 11. Medication trends in Nursing Homes in 2003, 2011, and 2017.

In NHs, the use of antipsychotic medication dropped from 42.7% to 32.7%, whereas in ALFs the use of antipsychotic medication increased from 27.3% to 34.0%. Also, the use of antidepressants dropped from 44.9% to 32.7% in NHs. In ALFs, the prevalence of antidepressants increased from 39.3% in 2007 to 46.3% in 2011 and dropped again to 37.5% in 2017. The prevalence of anxiolytic use dropped from 40.9% to 14.4% in NHs and in ALFs from 24.1% to 9.6%. The use of hypnotics also decreased significantly in NHs, from 11.3% to 6.1%, whereas in ALFs there was a significant increase from 10.2% to 17.2% (Figures 11 and 12).

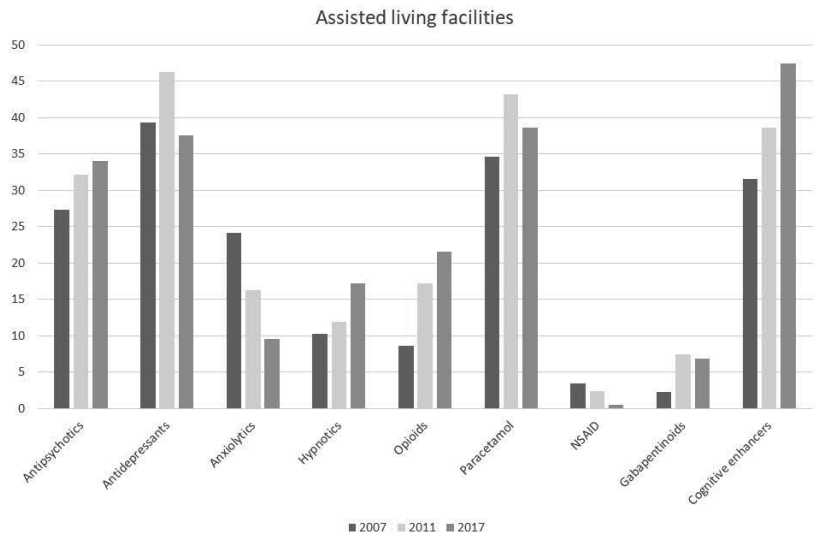


Figure 12. Medication trends in Assisted-Living Facilities in 2007, 2011, and 2017.

The prevalence of regular opioid use increased linearly in both NHs and ALFs over the years ($p < 0.001$). In NHs, the prevalence of regular opioid use increased from 11.7% in 2003 to 30.2% in 2017. In ALFs, the increase was from 8.6% in 2007 to 21.6% in 2017. The largest increase in prevalence was observed in strong opioids in NHs, where the prevalence increased from 1.9% to 14.9% (Figures 11 and 12).

When psychotropic drug users were stratified according to diagnosis of dementia, in NHs both people with and without dementia showed a significant decrease in the prevalence of psychotropic use over the 14-year follow-up period ($p < 0.001$ for cohort), whereas people with dementia used fewer psychotropics ($p < 0.001$ for dementia), and among these the use decreased more rapidly ($p < 0.001$ for interaction). There was no similar interaction in ALFs ($p < 0.001$ for cohort, $p=0.004$ for dementia, $p=0.41$ for interaction) (Figure 13).

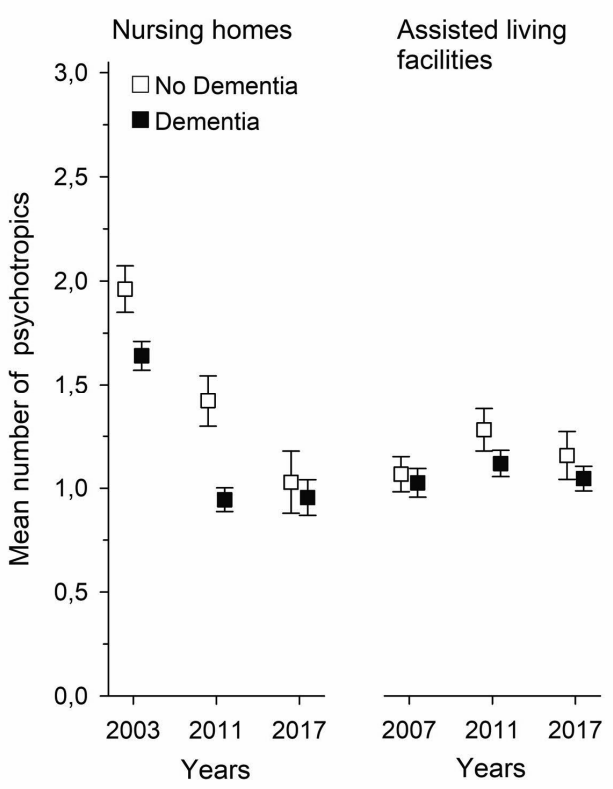


Figure 13. Mean number of psychotropics used by NH and ALF residents with and without dementia from 2003 to 2017.

When opioid users in NHs were stratified according to diagnosis of dementia, the entire cohort showed a significant increase in the use of opioids over the 14-year period ($p < 0.001$ for cohort). People with dementia used fewer opioids ($p < 0.001$ for dementia), and the use increased more rapidly among them compared with those without dementia ($p < 0.001$ for interaction). In ALFs, the residents with dementia used fewer opioids, but the use increased over time; there was, however, no interaction ($p < 0.001$ for cohort, $p < 0.001$ for dementia, $p=0.65$ for interaction) (Figure 14).

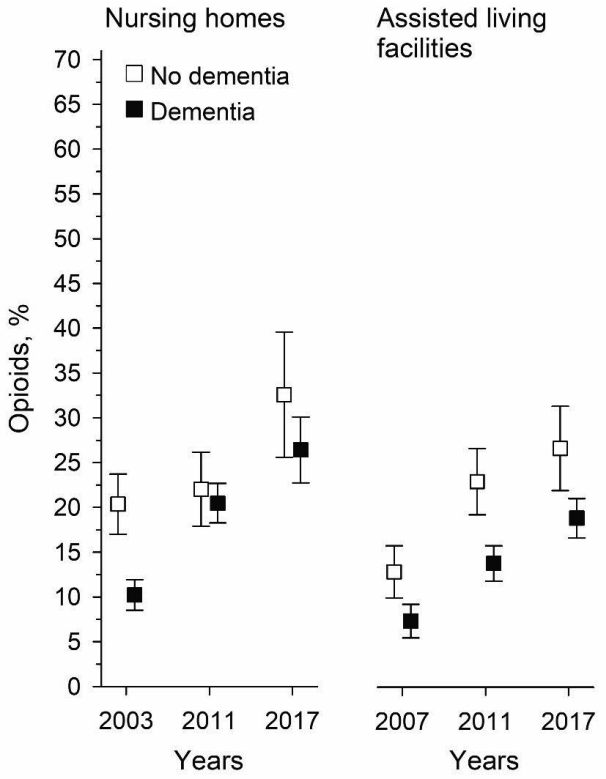


Figure 14. The percentage of opioid users among NH and ALF residents with and without dementia from 2003 to 2017.

5.5 ASSOCIATIONS BETWEEN NPSs, DEMENTIA AND HRQoL (STUDY III)

Study III concerned the association between NPSs and HRQoL, and, further, how the severity of dementia modifies this relationship. Residents were divided into three groups according to their NPSs (no significant NPSs (NPI scores 0–3), low NPS burden (NPI 4–12), and high NPS burden (NPI > 12).

The groups did not differ in their stage of dementia, MMSE and MNA scores, frailty or use of psychotropics. However, the high-NPS-burden group had the best mean BI score and represented the largest proportion of people using anticholinergic drugs. (See Table 1 in Article III).

Residents with severe dementia and with higher NPI scores had better HRQoL according to 15D data than respective residents with lower NPI scores. Residents with severe dementia (CDR 3) had worse HRQoL than residents with mild–moderate dementia (CDR < 3). In addition, there was a significant interaction between NPI scores and CDR ($p = 0.037$ for NPI, $p < 0.001$ for CDR, $p < 0.001$ for interaction adjusted for age, sex, and Charlson Comorbidity Index) (Figure 15).

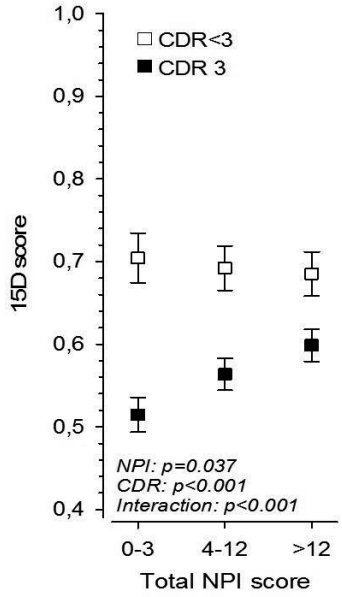


Figure 15. Relationship between total Neuropsychiatric Inventory (NPI) score and Health-Related Quality of Life (15D score) in two CDR according to Clinical Dementia rating (CDR)

HRQoL was worst for residents with severe dementia and a low NPI total score (0–3) and best for residents with mild–moderate dementia and a low NPI score (0–3).

In residents with severe dementia, HRQoL correlated positively with all NPS subgroups. Thus, the higher the HRQoL, the more NPSs in each subgroup. In residents with mild–moderate dementia, HRQoL was not significantly correlated with any of the NPS subgroups (Figure 16).

In severe dementia, higher NPI scores correlated positively with functional dimensions of the 15D instrument (mobility, usual activities, eating, speech, excretion and mental function), as well as vitality, whereas in mild–moderate dementia lower NPI scores correlated with lower levels of distress and depression as well as vitality (Figure 17).

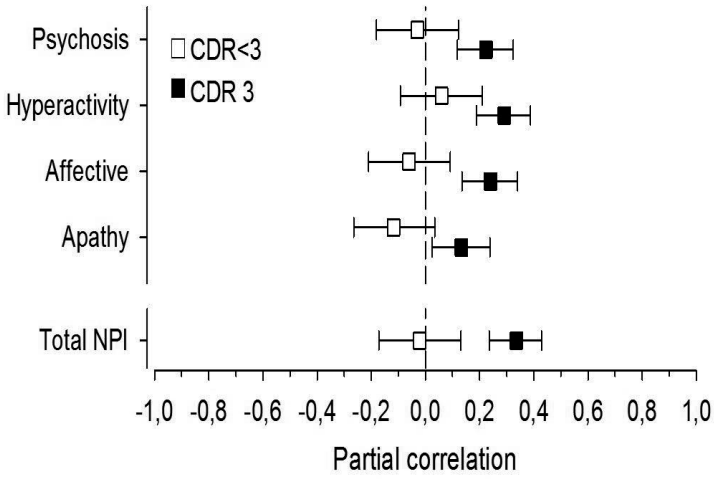


Figure 16. Partial correlation between health-related quality of life (HRQoL) (15D) and Neuropsychiatric Inventory (NPI) subsyndromes according to clinical dementia rating (CDR). Correlation adjusted for age, sex, and the Charlson Comorbidity Index.

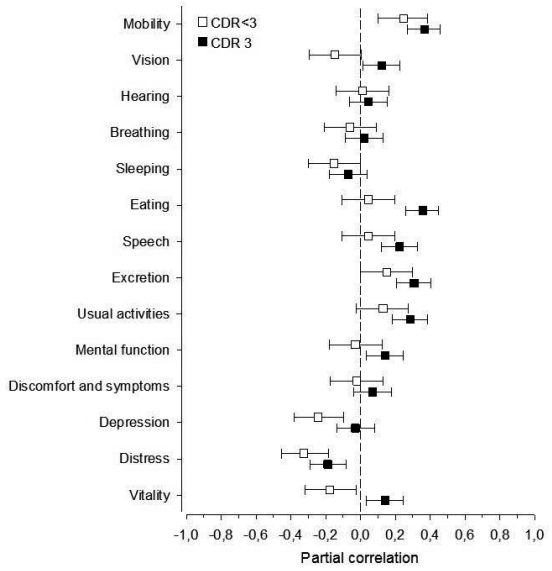


Figure 17. Partial correlation between total Neuropsychiatric Inventory (NPI) score and dimensions of 15D according to clinical dementia rating (CDR). Correlation adjusted for age, sex, and the Charlson Comorbidity Index.

6 DISCUSSION

6.1 MAIN FINDINGS

The present study concerned the relationships between NPSs, falls, psychotropic medication use and HRQoL in older adults with dementia.

Results from both Study I and Study IV showed that NPSs and their severity are associated with fall risk. According to Study IV, psychotropic drug use does not modify this association. In Study I a long-term exercise intervention program reduced the risk of falling related to NPSs in individuals with AD. The risk of falling increased linearly with NPI score in the control group, but exercise eliminated this risk in the intervention group.

Study II showed significant trends in the use of psychotropic medication and opioids over the past 14 years in long-term care in Helsinki. The prevalence of psychotropic medication decreased significantly in NHs, but not in ALFs. There was a considerable increase in the prevalence of opioids in both settings over time. Surprisingly, residents with dementia used fewer psychotropics and opioids and had a lower sedative load than residents without dementia. The study also showed important changes in resident profile. Both dementia and mobility disabilities were more prevalent and more severe in latter cohorts and the difference between these two settings diminished over time.

Study III showed that the severity of NPSs and the severity of dementia are both significant factors determining HRQoL and there is significant interaction between the two factors. A higher total NPI score was associated with better HRQoL in residents with severe dementia, whereas among those residents with mild–moderate dementia this association was not seen.

6.2 INTERPRETATION OF THE RESULTS

The results of Studies I and IV concerning the association between NPSs and falls are in line with those of the few previous studies (Hasegawa et al. 2010, Suzuki et al 2012, Sylliaas et al. 2012, Galik et al. 2018, Sato et al. 2018). Our results strengthen the existing evidence that NPSs are independent risk factors of falls. According to Study IV, the fall risk related to NPSs in long-term-care residents seems to particularly arise from hyperactivity and psychotic symptoms. This is in line with the findings of Suzuki et al., who noted that paranoid and delusional ideation, activity and affective disturbances, anxieties and phobias, and total NPI score were significantly higher among participants who fell (Suzuki et al. 2012). A population-based study carried out in Sweden in 2005 also showed that having hyperactive symptoms was one of the factors most strongly associated with falls (Kallin et al. 2005). The results of earlier studies regarding wandering are contradictory. A systematic review published in 2013 revealed wandering to be protective against falls (Kröpelin et al. 2013), whereas more recent studies have suggested that wandering increases the risk of falls (Sato et al. 2018, Ali et al. 2016). In our study, affective symptoms and apathy were not associated with an increased fall risk. This could be a result of less day-time activity, offering fewer opportunities for falling.

In accordance with the results of earlier studies, NPI scores among study participants were relatively low, the mean NPI total score being 14.7 among home-dwelling AD patients in Study I and 12.0 among long-term-care residents in Study IV. This is consistent with the results of other studies carried out in long-term care settings (Wetzels et al. 2010, Klapwijk et al. 2016, Ballard et al. 2018, Husebø et al. 2019), but studies of home-dwelling people with dementia have shown higher NPI scores (Conde-Sala et al. 2016, Hongisto et al. 2018). The FINALEX study was originally designed to improve physical functioning, so neuropsychiatric measures were secondary endpoints of the study. Thus, the study was not primarily designed to investigate or alleviate NPSs and thus may suffer from a floor effect.

Data from an earlier study showed that FINALEX exercise intervention did not decrease NPSs measured by NPI total score (Öhman et al. 2017). Thus, the mechanism behind the interaction of exercise, NPSs, and falls was probably connected to the beneficial effects of exercise on muscles and balance. It was also shown in a previous article concerning the FINALEX study that people with advanced dementia in particular – those suffering more often from hyperactivity, psychosis and fall risk – benefitted more from exercise compared with those with mild dementia (Öhman et al. 2016). Another potential mechanism to consider is improvement in executive functioning as a result of exercise intervention, as reported in an earlier study examining the effects of exercise on cognition (Öhman et al. 2017).

The results of Study II are in line with those of other studies concerning the growing trend of opioid use in institutional settings (La Frenais et al. 2018, Sandvik et al. 2016). However, opioid use in Helsinki is still lower than among disabled Medicaid beneficiaries in the US (La Frenais et al. 2018). In contrast to the results of a previous Finnish register-based study among community-dwelling older adults (Hamina et al. 2017), the use of opioids was lower among people with dementia than among those without. The increased use of opioids may reflect the global "opioid epidemic" (Humphreys 2017). On the other hand, in end-of-life care, the use of opioids and psychotropics is often appropriate and it has also been noted that pain assessment and management are suboptimal among patients with dementia in long-term care (Lichtner et al. 2014). The data from our study does not indicate the symptoms for which the opioids were used. The changes detected in the use of medication may partly reflect the changes in the resident profile, as both dementia and mobility disabilities were more prevalent and more severe in latter cohorts. It is known from Statistics Finland's statistics on the population structure that the number of older adults has grown significantly over the last 15 years. According to these statistics there were 600,000 persons aged at least 70 at the end of 2003 and 874,314 persons aged at least 70 in Finland at the end of 2019 (Official Statistics of Finland, 2019). At the same time, the proportion of older adults in long-term care has decreased. In Helsinki in 2000 12% of people aged at least

75 were in long-term care: 9.9% in NHs and 2.1% in ALFs, compared with 2.4% in NHs and 6% in ALFs in 2017 (Finnish Institute for Health and Welfare, 2019).

In Study III, surprisingly, in residents with severe dementia a higher total NPI score was associated with better HRQoL, whereas among those residents with mild–moderate dementia this association was not seen. In severe dementia, better HRQoL correlated with higher points in all neuropsychiatric subsyndromes. This result contrasts with those of most previous studies, in which it has been shown that having NPSs impairs quality of life (Hurt et al. 2008, Wetzels et al. 2010, Klapwijk et al. 2016, Hongisto et al. 2018). There are several explanations for this. One important thing to consider concerns the differences between the various QoL instruments used in different studies. In our study we used 15D. Several dimensions of 15D measure physical functioning. In severe dementia, higher NPI scores correlated positively with functional dimensions of 15D (mobility, usual activities, eating, speech, excretion, and mental function) as well as vitality, whereas in mild–moderate dementia lower NPI scores correlated with lower levels of distress and depression as well as vitality. Another possible explanation concerns the study population. In Study III, the cognition of the residents was relatively low, the mean MMSE score being 6.8. Thus, one explanation for why the results differ from those of most previous studies could to some extent be related to the characteristics of the study population. To the best of my knowledge, only one earlier study on quality of life in nursing-home residents (van der Zon et al. 2018) revealed a positive correlation between a higher NPI score and the course of quality of life. In that study the cognition of the residents was also low, the mean MMSE score being 7.1, which is similar to that in Study III.

6.3 STRENGTHS AND LIMITATIONS

Study I was a secondary analysis of the original FINALEX trial. It has several strengths. An RCT is the gold standard for measuring the effectiveness of an

intervention. Although no study is likely on its own to prove causality, randomization reduces bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome. Although the current study combined two intervention groups and was not an intention-to-treat analysis, the comparison groups were similar at baseline. In the FINALEX trial every participant had a confirmed diagnosis of AD. The exercise interventions were simple and clearly described. Adherence to the intervention was high, and the outcome measures were valid (Pitkälä et al. 2013). The participants' spouses recorded falls in daily fall diaries, which is a method that is highly sensitive in accurate recording of falls (Hannan et al. 2010).

The study also has some limitations that should be considered when interpreting the results. All participants were community-dwelling Caucasians living with their spousal caregivers. Because older couples were recruited, and men are more likely to have a surviving spouse, two-thirds of the participants with AD were men. Some limitations in external validity may also exist, as the participants were motivated volunteers living in their own homes in an urban area. Generalizing these results to other groups of individuals with AD should be carried out with caution. Nevertheless, there is no study that is completely representative of a population, and the baseline characteristics were similar to those in previous studies of people with dementia, supporting the generalizability of the results in this group. As mentioned above, this was a secondary analysis of the original trial. Neuropsychiatric measures were secondary endpoints of the study, so NPS scores were low at baseline. An additional limitation is that the FINALEX study was not double-blinded, thus exposing the study to a risk of bias. However, the outcome assessors were blinded to group allocation and they were unaware of the precise study question. Use of psychotropic medication can be a possible confounder as regards falls and thus the analysis was adjusted for psychotropic drug use.

In Study II the major strengths are the large sample size and comparable data collection at each of the four time points. Residents were assessed by well-trained nurses familiar with the residents in 2003, 2007, 2011, and 2017, and

they used the same data-collection instruments and methodology, resulting in high validity of the data. Another strength of the study is that medication use was taken directly from each resident's medication administration chart, ensuring that only the medication actually taken was included in the analysis. Medication was classified with ATC codes, an international classification system that allows comparison (WHO 2020). Moreover, we only considered medication that was taken regularly. However, it has been shown that psychotropic medication may also be administered as needed on a *pro re nata* basis, so our results might underestimate the actual use of these types of medication (Allers et al. 2017). Including psychotropics administered only on request may have led to different results.

In Study II we were not able to follow the same resident at different time points because the mean time spent in long-term care in Helsinki is less than two years. Another limitation is that response rates have significantly decreased over the years in NHs. Non-responders are mainly people with moderate–severe dementia and no proxy. Thus, estimates of increases in dementia and disability are probably underestimates. In addition, the organization of long-term care in Helsinki has changed over time, challenging the comparability of NHs. The number of NH beds has significantly decreased, whereas the increasing number of beds in ALFs has replaced them. However, all available residents living in long-term care in Helsinki were included.

In Studies III and IV important strengths are the relatively large representative sample and the use of well-validated measures. Long-term-care residents were assessed by trained study nurses, increasing the reliability of the results. Eighteen of the 54 nursing homes in Helsinki were included.

Limitations of Study III include the cross-sectional nature of the study, which allows us only to refer to associations within the study population but not to draw conclusions of causality, as epidemiological cohort studies can only demonstrate associations. Care-staff rating of residents' HRQoL may also be considered a limitation. However, this method was deliberately chosen

because of the high prevalence of severe dementia, which could have compromised the residents' self-reporting. 15D can also be rated by a proxy (Sintonen 2001). It is known from previous research that there are differences between proxy- and self-rated quality of life (Hurt et al. 2008, Beerens et al. 2013). Residents tend to consider their quality of life as being greater than do caregivers. Assessments of residents were performed by the member of staff who knew each particular resident best, in order to increase the validity of the data. The study population was made up of long-term-care residents with advanced dementia and, therefore, the results cannot be generalized to other populations with dementia. Even though the CDR scale is one of the most well-known and well-studied dementia-staging instruments, it is, however, not without limitations. A CDR score addresses both cognition and physical functioning, but it may also be influenced by physical comorbidities (Juva et al. 1995). Another limitation is that pain and use of physical restraint, possible confounders, were not assessed in our studies. It is well known that despite clear evidence of a lack of effectiveness and safety, physical restraints are frequently used in nursing homes and their use is associated with falls (Foebel et al. 2016, Lam et al. 2017). Another limitation is that only regularly used psychotropic medication was considered in our study. Psychotropics administered as needed on a *pro re nata* basis may have had a different impact on falls and their consequences.

Study IV, as a longitudinal follow-up study of a special cohort, is less susceptible to selection bias, because the cause always precedes the outcome (Hartung et al. 2009). However, we cannot rule out of confounders affecting both NPSs and falls. A major challenge, though, is patient follow-up. Loss of follow-up within a cohort can be a major source of selection bias, because participants who drop out do so for a reason that is unlikely to be random. In Study IV approximately a third of the participants died before the end of the follow-up year: 28.7% in the group with no significant NPSs, 33.2% in the low-NPS-burden group, and 33.7% in the high-NPS-burden group (p=0.56). However, all these participants' falls were also recorded during their follow-

up. However, we cannot rule out unknown confounders having an effect on the results.

In Studies I, III and IV only the NPI was used to assess NPSs. Thus, no efforts were made to rule out delirium, which might be common in this population. It has been shown in a previous study that NPSs and delirium overlap (Hölttä et al. 2011). Delirium is a major risk factor of falls (Sillner et al. 2019).

7 CONCLUSIONS

Neuropsychiatric symptoms and their severity are associated with fall risk among people with dementia – both among home-dwelling people and residents living in long-term care. Evaluation of NPSs, especially their severity, and neuropsychiatric subsyndromes should be part of comprehensive assessment when aiming to prevent falls in long-term-care residents with cognitive impairment. Use of psychotropic drugs did not modify the relationship between NPSs and falls among older people with cognitive impairment in long-term care.

Exercise has the potential to reduce the risk of falls associated with NPSs in dementia. Long-term and frequent exercise significantly decreased the number of falls.

The prevalence of psychotropic drug use has decreased over the last 14 years in NHs in Helsinki, but at the same time the rates of opioid use have increased in both NHs and ALFs, leading to a high overall sedative load among long-term-care residents.

Levels of severity of both neuropsychiatric symptoms and dementia are important determining factors of health-related quality of life. NPSs have a distinct impact on HRQoL at different stages of dementia. Whereas all neuropsychiatric subsyndromes (psychosis, hyperactivity, affective, apathy) correlated positively with 15D scores in severe dementia, no such relationship was seen in mild–moderate dementia.

8 IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH

The results of this study indicate that evaluation of NPSs, especially their severity, and neuropsychiatric subsyndromes, should be part of comprehensive assessment when aiming to prevent falls in long-term-care residents with cognitive impairment.

Regular exercise should be promoted as part of good-quality dementia care, as exercise has the potential to reduce the risk of falls associated with NPSs in dementia.

All sedative drugs including opioids should be evaluated when assessing the risk of falling in older adults with dementia. Psychotropic drugs continue to be commonly used in long-term care in Finland and the use of opioids is rising. Long-term-care staff should be trained as regards the adverse effects of all types of CNS medication in order to reduce various risks related to their use.

Neuropsychiatric symptoms are associated with HRQoL. Its evaluation should be interpreted in the light of a patient's stage of dementia, as the association between NPSs and HRQoL is different at later stages of dementia.

Neuropsychiatric symptoms represent a still scarcely explored topic in long-term-care settings, in which they are the most prevalent. Such settings would be ideal when considering RCTs related to alleviation of NPSs. Outcomes should include NPI scores, falls, QoL and caregiver stress. In addition, an RCT exercise study, similar to FINALEX, should be repeated in long-term-care settings, to see whether or not exercise can reduce falls in older adults with more severe cognitive impairment.

Further research is also needed to determine the factors explaining the different relationships between falls and various neuropsychiatric subsyndromes such as apathy and hyperactivity. This could be done using activity-sensor technology, allowing the total amount of physical activity to be measured. Activity monitors would be ideal in determining how much long-term-care residents actually move in normal days. Repeated cross-sectional studies in long-term-care facilities should continue and residents' falls, NPSs and HRQoL should be assessed in addition to nutrition, comorbidities, use of medication and functioning.

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